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A SYSTEM OF MEDICINE

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A
SYSTEM OF MEDICINE

BY MANY WRITERS

EDITED BY

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VOLUME IV

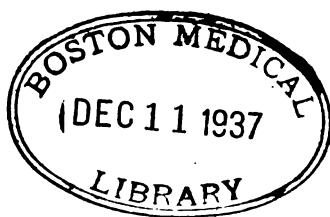
PART I

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PREFACE

THE fourth volume of the original *System of Medicine* has now been divided into two. The sections on Diseases of the Nose, Pharynx, and Larynx, which were originally condensed into 200 pages, have been removed, and now, greatly expanded and accompanied by a section on Diseases of the Ear, appear in a separate volume as Part II. of Vol. IV.

The present instalment, Part I. of Vol. IV., which contains the Diseases of the Liver, Pancreas, Ductless Glands, and Kidney, has undergone the following very considerable changes. Dr. Keith writes on the Anatomy of the Liver, and in the new article on Hepatoptosis supplements, as far as the Liver is concerned, the more general article on Visceroptosis in Vol. III. Dr. William Hunter has supplied a new article on Delayed Chloroform Poisoning; and the various diseases connected with the blood-vessels of the liver, including Multiple Abscesses and Suppurative Pylephlebitis, have been described by Dr. Herringham. Tropical Abscess of the Liver has already been dealt with in Vol. II. Part II. Dr. H. P. Hawkins has rewritten his account of Portal Cirrhosis, and a new article on Biliary Cirrhosis has been contributed by Dr. Morley Fletcher. Articles on Tuberculosis and Syphilis of the Liver have been provided by Dr. Hale White and Dr. H. P. Hawkins. In place of the valuable contribution to the first edition by Dr. Fitz of Boston, U.S.A., new articles on Diseases of the Pancreas have been written by Dr. Bosanquet and Dr. Newton Pitt.

A scientific classification cannot be completed until our

knowledge is complete; and as at present we have not material even for a provisional order in a scientific sense, it is best to be guided by convenience. It is for convenience that we append to the section on the Diseases of the Ductless Glands some other conditions, namely, Infantilism, Obesity, Adiposis Dolorosa, and Oedema.

The articles dealing with affections of the Thyroid Gland have undergone extensive change: Prof. George R. Murray has written an entirely new account of Myxoedema; and Dr. Hector Mackenzie has almost rewritten the other articles. Acromegaly, now described by Prof. Trevelyan, finds a place among diseases of the Ductless Glands; and a new article on the difficult subject of Status Lymphaticus has been written by Dr. John Thomson, who also deals with Infantilism. It has been thought advisable to include Adiposis Dolorosa, now succinctly described by Sir Dyce Duckworth, in close association with Obesity, and not far from Myxoedema. Prof. Halliburton's new article on Oedema is inserted here, so as to be conveniently placed with regard to the diseases to which it refers, namely, those of the Kidney and Liver in this volume, those of the Peritoneum in Vol. III., and those of the Pleura and Heart in Vol. V.

This volume, which is not quite so long as its predecessors, concludes with the Diseases of the Kidney. The important new article on Nephritis, by Prof. J. Rose Bradford, takes the place of the article in the former edition on Diseases of the Kidney characterised by Albuminuria, by Dr. Dickinson. The article on Other Diseases of the Kidney, which are on the somewhat shifting borderland between Medicine and Surgery, has been somewhat expanded by Mr. Henry Morris, who has added a section on Malformations and Diseases of the Ureter.

To Dr. A. J. Jex-Blake, who has compiled the Index, we are much indebted for a number of corrections in this and previous volumes.

CLIFFORD ALLBUTT.
H. D. ROLLESTON.

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In order to avoid frequent interruption of the text, the numbers indicative of items in the lists of "References" are only inserted in cases of emphasis, where two or more references to the same author are in the list, where an author is quoted from a work published under another name, or where an authoritative statement is made without mention of the author's name. In ordinary cases an author's name is sufficient indication of the corresponding item in the list.

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JAUNDICE.

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OF THE HEPATIC ARTERY.

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CIRRHOSIS.

PORTAL

BILIARY.

TUBERCULOSIS.

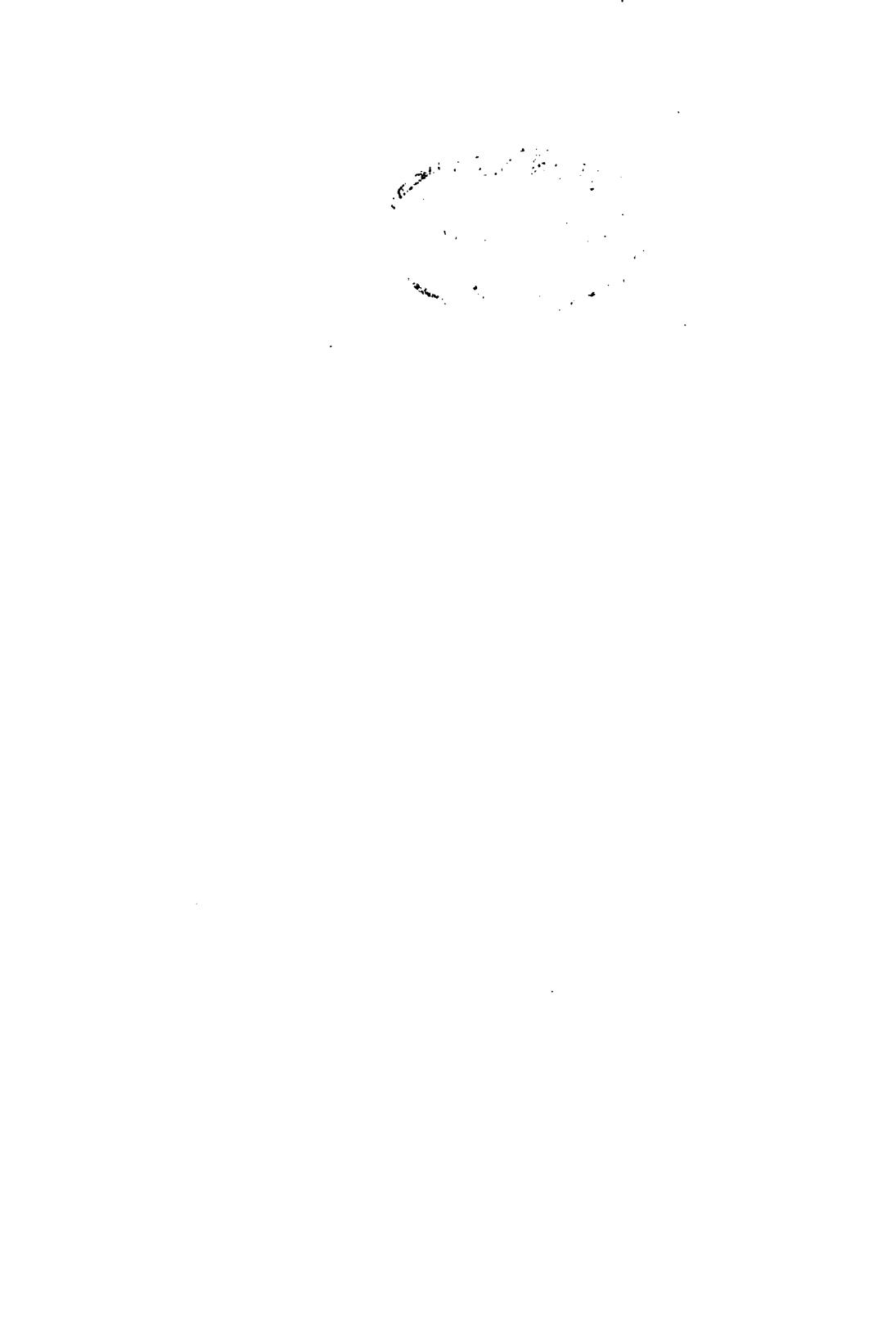
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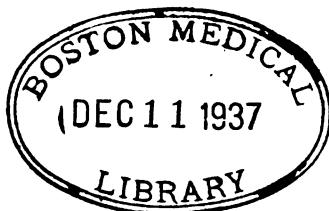
TUMOURS.

DISEASES OF THE GALL-BLADDER AND

BILE-DUCTS.

GALL-STONES.





ANATOMY OF THE LIVER

By ARTHUR KEITH, M.D.

Position.—When viewed from the front, the liver in its normal position in the body has a triangular outline, its apex being just under the apex of the heart, while its base lies against the right side of the thorax from the 8th to the 11th ribs (Fig. 1). The best method of marking out the average position of the *upper border* of this hepatic triangle on the surface of the body is to take three points (see Fig. 1). (1) One on the 5th rib of the right side vertically below the nipple or mid-point of the clavicle; this marks the level of the highest point of the liver in a position of expiratory rest, and may be named the *upper hepatic point*; (2) a point $\frac{1}{2}$ an inch (10 to 15 mm.) below the sterno-*ensiform* junction, which is marked by a depression below the sternal ends of the 7th pair of cartilages; (3) a point immediately below the apex beat of the heart. By joining these three points the upper border of the liver is indicated. As the upper border passes to the right of the nipple line it sinks downwards, so that in the mid-axillary line it falls to the lower border of the 8th rib. Since the 5th rib is sometimes difficult to recognise and often varies in shape and position, it is found as a matter of practice to be more accurate and easier to use the *sterno-ensiform* line to indicate the normal upper level of the liver (Fig. 1). This line, which crosses the 5th rib when the thorax is normal in shape, traverses the trunk at the junction of the sternum with its ensiform process. Using this line as a base, it is easy to estimate accurately the extent to which the upper border of the liver may be displaced upwards or downwards in abnormal conditions of that organ. Examination of a series of healthy individuals shews that the upper border of the liver varies from 10 mm. above to 15 mm. below the sterno-*ensiform* plane in the right nipple line.

The *lower border* of the liver is best indicated by joining the following four points (see Fig. 1):—(1) Apex point, below apex of heart; (2) mid-epigastric point, which is midway between the umbilicus and the sterno-*ensiform* point; (3) right costo-rectal point, situated where the outer border of the rectus crosses the costal margin; here is situated the fundus of the gall-bladder; (4) the tip of the 11th rib, which is easily

recognised by its occupying the lowest part of the costal margin (Fig. 1). When viewed from the right the 11th rib is seen to have an important relation to the liver (Fig. 2); it corresponds to its right lower margin. Along the line of the eleventh rib the liver is in contact with the right kidney and hepatic flexure of the colon (Fig. 2). It should be remembered that the liver varies greatly in shape, volume, and position even in healthy individuals. The indications given above are founded on the examination of a large number of young adults—mostly men.

Surfaces and Relations.—There are but two surfaces on the liver, a visceral and a parietal. The *visceral* surface is in contact from left to right with the following structures: the lesser curvature and a limited area (about one-fifth) of the upper surface of the stomach; the gastro-

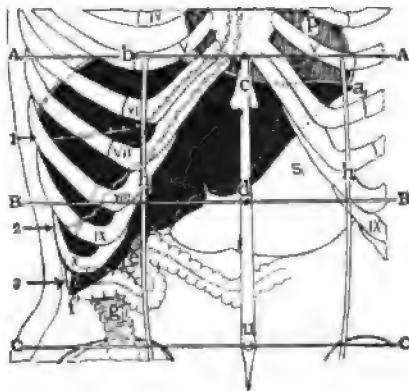


FIG. 1.

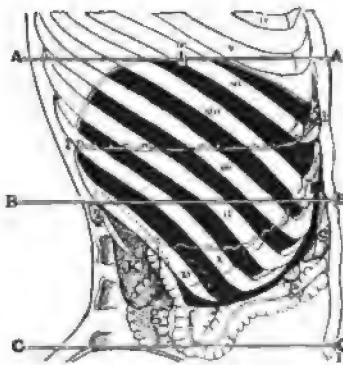


FIG. 2.

FIG. 1.—The normal position of the liver, viewed from the front.
FIG. 2.—The normal position of the liver, viewed from the right side.

A-A', Sterno-ensiform line or plane. B-B', Transpyloric or mid-epigastric plane. C-C', Umbilical plane. 1, Lower border of lung ; 2, lower border of pleura ; 3, tip of the 11th rib. a, Apex of liver ; b, upper hepatic point ; c, point 10 mm. below sterno-ensiform plane, marking the usual level of the central part of the diaphragm ; d, mid-epigastric point ; e, on colon below fundus of gall-bladder ; f, hepatic flexure of colon ; g, ascending colon ; h-h', linea semilunaris ; i, level of the right dome of diaphragm as seen from the side ; k, right kidney ; l, pericardium ; m, stomach ; u, umbilicus.

hepatic omentum which intervenes between a part of the pancreas and the under surface of the left lobe of the liver; the pylorus, the first stage of the duodenum, the gall-bladder, hepatic flexure of the colon, and commencement of the transverse colon; the upper half of the right kidney, and the right suprarenal. By these structures an irregular shelf is formed, sloping forwards, downwards, and to the right, on which the *visceral* surface of the liver rests. The *parietal* surface is convex and in contact with the abdominal parietes, one-fifth being in contact with the anterior abdominal wall (Fig. 1), and four-fifths with the diaphragm. The *parietal* surface is covered with peritoneum everywhere except over an area about the size of the palm of the hand, on the posterior surface, where it is bound to the diaphragm by connective tissue and surrounded by a reflection of

peritoneum, this bond forming the mesohepar—a name much to be preferred to the loosely defined coronary ligament.

The *relations* of the liver to the right lung and pleura are worthy of close attention. The part of the liver in the right hypochondrium is divisible for clinical purposes into three zones, each of which may be accurately defined; an upper or pulmonary zone is separated from the thoracic wall by the concave base of the right lung (Figs. 1 and 2), a middle or pleural zone by a reflection of the pleura only, and a lower or non-pleural zone by the diaphragm alone. These three zones are marked out on the surface of the body as follows: the pulmonary zone extends from the level of the sterno-ensiform plane to the *pulmonary line*, which indicates the lower border of the lung; the pulmonary line corresponds to the 6th costal cartilage and to a line drawn from the heel or bend of that cartilage (see Fig. 1) horizontally round the body to the mid-line behind; the pleural zone lies between the lower border of the lung and the line of reflection of the pleura—the *pleural line*. This line corresponds to the 7th costal cartilage as far as its bend or heel; from there the line descends somewhat (about $1\frac{1}{2}$ inch, or 25-30 mm.) to a point 2 inches or 50 mm. (varying from 40 to 60 mm.) above the lowest point of the costal margin (Fig. 1), and from there it ascends as it passes backwards to the level of the 12th dorsal spine. The non-pleural zone lies between the pleural line and costal margin. It is a crescent-shaped space (Figs. 1 and 2) about 2 inches (50 mm.) in height at its deepest part, but I found that its depth varied from $1\frac{1}{2}$ to $2\frac{1}{2}$ inches (30 to 60 mm.) in a series of even 20 subjects.

Percussion of the Liver.—The area of absolute liver dulness corresponds to the pleural and non-pleural zones, and to the epigastric area of the parietal surface (Figs. 1 and 2). The area of absolute hepatic dulness is triangular in shape, measuring $4\frac{1}{2}$ to $4\frac{3}{4}$ inches (110 to 120 mm.) in height in the mid-axillary line and 4 to $4\frac{1}{2}$ inches (100 to 110 mm.) in the nipple line. These measurements were obtained on healthy medical students. In the female the vertical extent is about $\frac{1}{2}$ inch (20 mm.) less. The area of absolute hepatic dulness merges with that of the cardiac dulness along the left half of the upper border of the liver. Frequently in children, and in one woman in five, the left lobe of the liver extends so far to the left as to reach, or even partly to overlap, the spleen. Such an extension yields a less resonant note as percussion is carried downwards from the resonance of the left lung to the tympanitic note yielded by the stomach. The lower border of the left lobe overlaps the stomach, and usually a marked alteration in the note is obtained in passing from the one organ to the other, but often the lower border of the liver is so thin that the change in the note is very slight. In gastroptosis, part of the gastrohepatic omentum and pancreas becomes exposed between the lower margin of the liver and the lesser curvature of the stomach, and gives a dull note on percussion, and this dulness may, if percussion only be relied on, be mistaken for an extension downwards of the liver. Below the 11th rib the dulness of the liver merges into that of the right

kidney. Occasionally a loop of the transverse colon passes between the anterior surface of the liver and the diaphragm, greatly diminishing the extent of the hepatic dulness. The dulness also disappears when gas escapes into the peritoneal cavity, as in perforation of a duodenal ulcer, unless the patient lies on the right side, or the liver is previously fixed by adhesions to the anterior abdominal wall.

Movements and Fixation of the Liver.—It is impossible to insist too strongly that the liver, in the living body, is subjected to a continuous positive pressure, which fluctuates from 3 to 7 mm. Hg in ordinary respiration up to 80 or 100 mm. Hg during active exertion. This pressure is caused and maintained by the tonus and contraction of the diaphragm acting over its convex parietal surface, and the tonus and contraction of the belly-wall muscles which maintain and press upwards the visceral shelf on which the under surface of the liver rests. In the normal body the ligaments take no part in suspending or supporting the liver; it is only when the natural support of the liver is withdrawn, as in visceroptosis, that the ligaments can so act. The liver is so attached that it may undergo extremely free respiratory movements. To one structure only is it firmly bound, namely, to the movable diaphragm; it is the *posterior* aspect of the parietal surface of the liver that is so fixed; and the gastrohepatic omentum, the falciform and round ligaments allow a free lateral and vertical movement. In ordinary respiration of the abdominal type the upper border of the liver, in the right dome of the diaphragm, undergoes a vertical movement varying from $\frac{2}{5}$ to $\frac{3}{5}$ inch (10 to 15 mm.); in forced respiratory movements the vertical range is from 2 to $3\frac{3}{5}$ inches (50 to 90 mm.). By the orthodiascope Dr. Halls Dally estimated that the total vertical movement of the right dome of the diaphragm is only 34 mm. With the vertical movement there is also a forward one of the right lobe, so that the liver undergoes a rotation round a vertical axis represented by the inferior vena cava (see Keith). The movements of the liver are restricted in those whose breathing is of the thoracic type; in them the liver is fixed by the contraction of the muscles of the abdominal wall and forms a fulcrum from which the diaphragm assists in raising the thorax. Besides the respiratory movements, the liver is also influenced by the filling and emptying of the neighbouring viscera; it is rotated towards the right (dextroverted) as the stomach fills. The stomach is relatively small in the newly-born and young; with age its size and cubic contents increase; the liver is pushed more to the right of the mid-line of the body, the left lobe at the same time undergoing a certain degree of atrophy. To the respiratory and gastric movements of the liver must be added those due to changes in the posture of the body. In passing from the supine to the erect attitude, the upper border of the liver sinks from $\frac{2}{5}$ to $\frac{3}{5}$ inch (10 to 15 mm.), the lower border from $\frac{3}{5}$ to $\frac{4}{5}$ inch (15 to 20 mm.), for with this change of posture there is also an alteration in the diameters of the thorax and of the liver. Enlargement of the thorax, such as occurs in emphysema, and gaseous distension of the

caecum, ascending or transverse colon, or small intestine, cause a tilting upwards and forwards of the lower border of the liver (*retroversion*).

Dimensions, Weight, Consistency, and Vascularity of the Liver.—The vertical diameter of the liver in the mid-axillary line in an average man is $6\frac{3}{4}$ inches (170 mm.); it varies from $5\frac{3}{4}$ to 8 inches (140 to 200 mm.); as a rule this measurement is $\frac{1}{4}$ inch (20 mm.) less in women than in men. The antero-posterior or coronal diameter of the right lobe varies from 55 to 70 per cent of the vertical height in normally formed individuals; in those in whom the liver has become anteverted, the back to front diameter is only 25 to 40 per cent of the vertical diameter. In the liver of the newly born the coronal diameter varies from 55 to 80 per cent. As to the average weight of the liver, Dr. Salaman gives 60 oz. (1700 grms.) as the mean for English males and $53\frac{1}{2}$ oz. (1530 grms.) for English females, with a variation of nearly 10 oz. (300 grms.) above and below the mean. Quincke gives 1500 grms. and Vierordt 1579 grms. as the mean for German males. Vierordt estimates that the liver forms 4·5 per cent of the weight of the body in the newly born and 2·7 per cent in the adult. The weight and volume of the liver depend largely on the degree to which its vessels are distended. Dr. Salaman observed that the normal liver could double its volume when water was injected by the portal vein at a pressure of 675 mm. of water, representing the pressure of blood in arteries. It is comparatively easy to inject 1200 c.c. into a normal liver, and it is surprising how little the diameters of the liver are increased by such an injection. In a series of five experiments the vertical diameter of the liver was only increased 12 mm. and the antero-posterior 10 mm.; the experiments by Glénard and Siraud shew similar results, and it will thus be seen that a considerable congestive enlargement of the liver may not be detected by clinical means. After death the liver feels firmer and more resistant to the touch. It is plastic, in the sense that it can be moulded to any form during life; experimental proof of this is given by the manner in which it yields to the pressure of corsets and of surrounding viscera. Its consistency is increased by fatty or lardaceous change, by an increase of its fibrous basis, and by distension of its vessels.

Congenital and other Deformities of the Liver.—Prof. Arthur Thomson has described the minor fissures which frequently occur on the liver and correspond to divisions found in the livers of various animals. These minor fissures are common, but occasionally specimens are found in which deep anomalous fissures separate the liver into lobes which have no correspondence with any known arrangement in the animal kingdom (see Rolleston). Compression grooves and sulci are frequently seen on that part of the upper surface of the liver which lies in the right dome of the diaphragm. They are directed coronally and vary from one to five in number, the chief one being situated immediately in front of the point where the inferior vena cava perforates the diaphragm; Moody refers to a specimen with nine grooves. They may or may not contain a fold of the diaphragm. They are folds formed by

a compression of the liver from side to side, usually the result of a deformity or compression of the lower half of the thorax, either from fibrosis of the lung, or more frequently by compression of the chest by corsets or belts. Hence these compression sulci occur eight times more frequently in women than in men. These sulci are of no clinical significance; examination of sections made across them shews that they are not due to an inflammatory contraction. In 58 cases examined by Séglas, there were only 5 in which the lungs appeared to be healthy.

There are three common types of *deformed liver*. (1) The anteverted type, in which the lower border, more especially of the left lobe, is depressed, so that the vertical diameter is increased, while the back-to-front diameter is markedly diminished (see Fig. 3, p. 14). (2) The dextroverted, in which the left lobe is either compressed into the right hypochondrium or atrophied, and the right lobe turned downwards, so that its lowest part projects into the right loin beneath the cartilages of the 10th and 11th ribs (see Fig. 3, p. 14). The vertical diameter is increased, while the side-to-side diameter is diminished. (3) The retroverted, in which the lower surface, instead of being directed backwards as much as downwards, is directed downwards; the anterior border of the visceral surface is on the same level as its posterior border, or even higher. The vertical diameter is diminished, while the back-to-front measurement is increased.

The anteverted and dextroverted types shew a constriction or groove at the level of the transpyloric plane (Fig. 1, *B,B₁*), usually caused by the use of corsets. This constriction does not correspond to the subcostal margin, but to a line crossing the 9th, 10th, and 11th ribs and cartilages in the transpyloric plane. The part of the liver below the constriction shews changes due to chronic venous engorgement, and at the level of the groove or constriction the lobules are atrophied to a greater or less degree, the bile-ducts, portal vessels, and hepatic veins greatly dilated, and the capsule of the liver grey and thickened.

Capsule and Fibrous Stroma of the Liver.—If the liver were supported from the diaphragm, as Faure erroneously supposed, the thin-walled hepatic veins should be strengthened by a fibrous coat, but this is not the case; they have no sheath. On the other hand, the ramifications of the portal vein, hepatic artery, and bile-duct are surrounded by a dense fibrous sheath—Glisson's capsule. It is not against downward but against forces acting in an upward direction, such as coughing, that provision has been made. Glisson's capsule also protects the glandular tissue of the liver from being compressed by the high pressures (60 to 100 mm. Hg) which may occur in the portal veins, gall-bladder, and bile-ducts during active movements of the body. The capsule of the liver is thin, elastic, and composed of a serous and a subserous layer, measuring 30 to 40 μ in thickness. Delicate processes pass into the liver to terminate in the ramifications of Glisson's capsule. Within the lobules (1 to 2 mm. in diameter) there is a reticular stroma composed of extremely delicate fibres.

Vessels of the Liver.—The sectional area of the hepatic artery is to that of the portal vein as 2 : 5. The hepatic artery supplies the fibrous stroma of the liver, its capillaries ending in the portal capillaries in the periphery of the lobules. On entering the transverse fissure the portal vein divides into right and left divisions. Mr. Cantlie has shewn by experiments, which I have verified, that the right division supplies the part of the liver situated to the right of a line drawn from the fundus of the gall-bladder to the inferior vena cava, the left division supplying the part to the left of the divisional line. The two divisions of the portal vein are terminal in the sense that it is impossible to force an injection either by the right or by the left branch of the vein across this line. The liver to the left of this divisional line may be completely atrophied (see Rolleston, p. 3), or the hepatic tissue along the divisional line may be atrophied, partially separating the liver into a right and left part. The intralobular capillaries commence in the interlobular ramifications of the portal vein and end in the sublobular tributaries of the hepatic veins, but the nature of the walls of these capillaries and their relation to the hepatic cells have been, and still are, matters of dispute. Minot shewed that these capillaries were sinusoids, that is, blood-spaces into which the developing hepatic epithelium had budded, and that therefore the cells were directly bathed with blood. There can be no doubt that the walls of the capillaries are extremely delicate, and appear on section as a cuticle bounding the hepatic cell. Here and there in the wall of the capillaries appear stellate (Kupffer's) cells, which are said to be phagocytic. The delicate wall of the capillaries appears to be formed of fine extensions of the stellate cells.

The Bile-Ducts.—The biliary capillaries commence in an intralobular network of extremely minute channels or spaces ($2\text{-}3 \mu$ in diameter) formed between adjacent cells. Ampullary extensions of the bile-capillaries within the hepatic cells have been demonstrated. On leaving the lobules, the bile enters the efferent system composed of ducts with fibrous coats, in which muscle appears as the transverse fissure is reached. They are lined by cubical epithelium and shew numerous crypts and diverticula, probably glandular in nature, and communications and cross anastomoses occur between the efferent channels. On the anterior aspect of the parietal surface of the liver, especially of the left lobe, numerous aberrant bile-ducts are found, which are probably the efferent channels of parts of the liver which have become absorbed during the life of the individual.

Lymphatics of the Liver.—Lymph flows from the liver in three streams. Much the largest stream leaves by the transverse fissure, and after passing through three or four glands situated in the gastrohepatic omentum in front of the portal vein and near the common bile-duct, and through another group of glands at the upper border of the pancreas, enters the receptaculum chyli. A second set of vessels accompanies the hepatic veins and perforates the diaphragm with the inferior vena cava, when it passes backwards to join the lymphatics of the posterior medias-

tinum, although some of the branches also anastomose with the efferent vessels of the third stream. This enters the diaphragm by the coronary and falciform ligaments, drains part of the convex surface of the liver, and ends in glands situated on the diaphragm behind the lower end of the sternum. The efferent vessels of these glands pass upwards with the internal mammary vessels. The subperitoneal and subpleural lymphatics of the diaphragm communicate extremely freely, and hence infradiaphragmatic infections may easily become supra-diaphragmatic or vice versa.

Nerves of the Liver.—The *phrenic* is the sensory nerve of the diaphragm, and is distributed on its under surface, supplying freely the mesohepar and other attachments of the liver; this explains the frequency of dull aching pain in the right shoulder in hepatoptosis, for Lennander has shewn that though the abdominal viscera are insensitive, dragging on their peritoneal attachments gives rise to pain. The *afferent* or *sensory nerves* of the liver reach the organ by the splanchnic nerves, semilunar ganglia, solar and hepatic plexuses from the 5th, 6th, 7th, 8th, 9th, and 10th dorsal segments of the cord, which also supply the skin, muscles, and parietal serosa over the liver. The chief is probably the 9th segment, for it is usually along the 9th nerve that tenderness is felt and pain referred to the abdominal wall. The ramifications of the hepatic artery and portal vein are freely supplied with *vaso-constrictor* and *vaso-dilator nerves* derived from the sympathetic system. Fibres also terminate on the bile-ducts and enter the lobules, but none have been traced to the liver-cells, and there is no evidence of the existence of fibres with a secretory function. The right vagus sends a small branch to the solar plexus, some of the fibres being traceable to the liver. Stimulation of the vagus causes contraction of the gall-bladder and main efferent bile-ducts, whilst inhibition follows stimulation of the sympathetic.

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A. K.

HEPATOPTOSIS

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THE name hepatoptosis was introduced by Glénard in 1892 to designate a condition of the liver which he found in 20 per cent of some 3500 patients presenting themselves for treatment at Vichy. As his diagnosis was mainly founded on recognition of prolapse of the lower border of the liver, it is clear that at least three distinct conditions were thus included:—(1) Depression of the lower border of the liver from general enlargement of the organ—as in diabetes, rickets, malaria, alcoholism, and in toxæmia of abdominal origin; (2) prolapse of the lower border of the liver from compression or constriction of the lower half of the thorax, usually produced by tight corsets or belts, but also by fibrosis of the lungs, spinal or thoracic deformities, or from the presence of the thoracic condition known as the *habitus phthisicus*; (3) prolapse of the whole organ to a greater or less degree, the upper border having sunk from 1 to 2 inches (25 to 50 mm.) below the sterno-ensiform plane (see Figs. 3 and 4), while the lower border has descended to even a greater extent below its normal position. To forms 1 and 2 Glénard applied the name of *partial hepatoptosis*, because he believed that they represented early stages of form 3, *total, complete, or true hepatoptosis*. The rapidity with which the partial may pass into the complete form is illustrated by Dr. Crawfurd's case of a woman aged sixty-five, confined to bed, in whom the lower border of the liver descended two inches in the course of three days, and the upper border to a corresponding degree. True hepatoptosis is never an isolated condition, but always part of a general sinking of the abdominal viscera—the condition now recognised as visceroptosis (see Vol. III. p. 860).

Of the various conditions included under the name hepatoptosis, two only are of real clinical significance—(i.) partial hepatoptosis with the formation of a Riedel's lobe; (ii.) true hepatoptosis accompanied by an abnormal mobility of the liver. A *movable, wandering, ambulatory, or migrating liver* represents the extreme degree of true hepatoptosis. Nearly all the cases reported in medical literature (some 120 in all) as hepatoptosis belong to the latter group. Here we propose to confine our attention to these two forms. The alterations in the liver in visceroptosis are described elsewhere (Vol. III. p. 864 *et seq.*). The common deformities of the liver are mentioned on pp. 7, 8. (For literature bearing on corset deformity, see Rolleston, Hertz, Hayem, Faure, Leue.)

I. PARTIAL HEPATOPTOSIS WITH THE FORMATION OF A LINGUIFORM PROCESS.—In 1888 Riedel drew attention to the frequency with which

disease of the gall-bladder is accompanied by a tongue-shaped extension of the part of the liver lying under the cartilages of the 10th and 11th right ribs. This *subcostal extension* or linguiform process is usually known as Riedel's lobe. A subcostal extension or process of the right lobe of the liver into the loin occurs in at least three forms, all of which were probably included by Riedel in his description of the linguiform lobe. There is (1) a prolongation downwards of the right lower angle of the liver, formed by the junction of the right lower border with the anterior lower border (see Figs. 1 and 2, p. 4, and Fig. 3), usually carrying with it the hepatic flexure of the colon; it may reach the iliac crest in the right loin; this form—the *angular*—occurs in the dextroverted liver (Fig. 3), and does not carry with it the gall-bladder. (2) The *marginal process* is a localised extension downwards of the lower margin of the right lobe usually carrying with it the gall-bladder. This form occurs in the anteverted liver (Fig. 3). (3) The *constriction process* or lobe is clinically the most important. It is a part of the right lobe constricted off by the pressure sometimes of the costal margin, but more frequently of the line of the waist. The zone of constriction forms a flaccid pedicle; the process is freely movable and may carry on it the gall-bladder, although this is not usually the case. Such a lobe may attain a large size; in the case of a woman, aged thirty-six, reported by Mr. C. Martin, a lobe of this kind was removed by operation and weighed 1680 grms., the weight of a normal liver.

Etiology.—There is no evidence that a subcostal lobe can be produced during the development and growth of the liver. All the data at our disposal point to the conclusion that the formation of the lobe is a result of a partial extrusion of the liver from the hypochondriac space, either because that space has been reduced by compression or deformity of the thorax so that it can contain a part only of the liver, or because the liver has so increased in size that it can no longer be contained in the hypochondriac space. At birth the breadth of the lower margin of the thorax is considerably more than the bi-iliac diameter of the pelvis. In the adult, on account of the formation of the waist and the growth of the pelvis, the bi-iliac diameter in many women becomes 50 to 75 mm. (2 to 3 inches) more than the breadth of the body at the waist. Hence when the lower part of the right lobe of the liver is extruded from beneath the costal margin, it expands into the wider space in the right loin above the iliac crest. If the liver be dextroverted, the angular process is formed; if anteverted, the marginal form is produced; if the waist is formed just above the subcostal margin, a constriction process appears. Riedel found that these processes disappeared when the condition of the gall-bladder was relieved, and regarded their formation as a direct result of biliary disease. In 1000 consecutive patients, Glénard found that a subcostal process was accompanied by a movable kidney in 11 men and 69 women. In 24 out of 41 cases of deformity of the liver, the gall-bladder was distended and enlarged (Hertz).

Symptoms.—A *linguiform process* of the liver, as a rule, gives rise to

no symptoms, the patient being unaware of its presence. The chief reason for recognising them is that they may not be mistaken for other conditions, such as a prolapsed right kidney, a distended gall-bladder, a tumour of the ascending or transverse colon, of the omentum, or of the pylorus.

A *constriction lobe or process*, on the other hand, may give rise to well-marked symptoms; the patient may complain of obscure dragging sensations in the region of the liver, of dull aching pains referred to the right hypochondrium or loin, or of tenderness when pressure is applied over the tumour. There may be acute attacks resembling biliary colic. The tumour can be palpated and moved in the right loin. The dulness, obtained on percussion over it, is continuous with that of the liver, except when the pedicle of the lobe has become so attenuated that the tympanitic note of the bowel is elicited between the dulness of the liver and that of the constriction lobe. The tumour follows the respiratory movements of the liver, and may be so freely movable when manipulated or when the posture of the body is changed that a large constriction lobe may be mistaken for a movable liver. Glénard considers that many of the cases reported as movable liver were really only cases of partial ptosis with a large movable lobe.

Treatment.—In most cases in which a subcostal process of the liver is recognised there are no symptoms, and therefore no need for treatment. When treatment is required, attention should be directed first to the condition of the gall-bladder; and cholelithiasis, or any of its numerous sequels, should be thoroughly treated. In the majority of cases the support afforded by closely fitting corsets, of the straight-fronted make or of the form designed by Gallant, will generally enable the patient to lead an active life without discomfort. The patient should apply the corsets while in the recumbent position. Although these means give relief in most cases of partial hepatoptosis, some cases prove intractable, especially those with a pedunculated subcostal lobe of considerable size. Two methods of operative treatment have been practised—(a) excision of the lobe; (b) its fixation to the abdominal wall and subcostal margin. Excision was first performed by Langenbuch in 1887; Bastianelli, C. B. Lockwood, Billroth, and Tscherning have reported successful results from this method of treatment (see Terrier). To obtain fixation of a movable lobe, the surgeon produces inflammatory adhesions, by the use of sutures of silk or catgut, between the lobe and the anterior abdominal wall, after the liver and its abnormal lobe have been pushed upwards as far as is possible. The three or four sutures employed may include the whole thickness of the lobe or be buried in the subcapsular tissue only of its anterior surface. Terrier reports favourably on this method of treatment, and gives a list of eight cases cured by fixation.

II. TOTAL HEPATOPTOSIS WITH ABNORMAL MOBILITY (*Movable* or *Wandering Liver*).—Landau classified the displacements of the liver into four groups—(1) the anteverted, (2) the lateroverted (dextroverted), (3) retro-

verted, (4) dislocated livers, divided into two—(a) fixed, (b) movable. The latter group (b) corresponds to that described here as total hepatoptosis

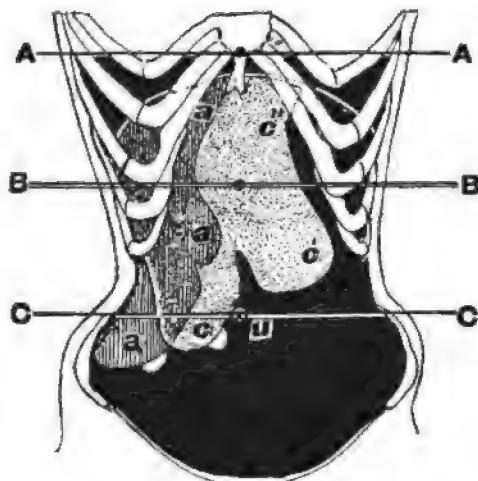


FIG. 3.—The dextroverted, *a*, *a*, *a*, and anteverted, *c*, *c*, *c*, forms of movable liver placed in the same subject for comparison. A, A, the sterno-ensiform plane; the domes of the diaphragm are seen to have sunk far below this plane. B, B, the transpyloric or mid-epigastric plane. C, C, umbilical. *a*, *a* represent the lower border of the dextroverted, and *c*, *c* of the anteverted liver. The border between *c* and *c*' is formed by the stretching of the extremity of the left lobe.

with abnormal mobility. Although he had not realised that displacement of the liver was only part of a general ptosis of the viscera, his observations are still of great service in connexion with the etiology of true hepatoptosis. In Fig. 4 the sagittal form of the anteverted liver is contrasted with that of the normal; it will be seen that the change is the result of a flattening of the liver from back to front more than of a rotation of the liver on a transverse axis formed by the mesohepar. In the dextroverted form, a rotation of the liver takes place round an antero-posterior axis, that axis being formed by the round ligament of the liver and the fibrous tissue of the ductus venosus. There is thus a fibrous cord of considerable strength running from the umbilicus to the foramen quadratum of the diaphragm along the under surface of the liver.

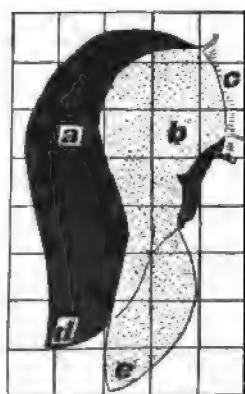


FIG. 4.—Sagittal section of the normal liver (*a*), and of the anteverted liver (*b*). C, the mesohepar; *d*, *e*, the lower borders of the normal and of the anteverted livers.

place in dextroversion. In the retroverted form, the posterior part of

the liver has descended $1\frac{1}{2}$ to $1\frac{3}{4}$ in. [30 or 40 mm.] below its normal position, while the anterior border has descended to a less or perhaps equal extent. The right crus of the diaphragm, to the upper part of which the liver is attached, measures only $1\frac{3}{4}$ to $2\frac{1}{2}$ in. [40 to 60 mm.] instead of 3 to $4\frac{1}{2}$ in. [75 to 110 mm.] in true hepatoptosis with retroversion. The crus is permanently contracted like the flexor muscles of the leg in pes equino-varus. Of these three forms assumed by the liver in true hepatoptosis, only the first and second—the anteverted and dextroverted—pass into the most extreme or movable stage. These two forms of movable liver are shewn in Fig. 3.

Etiology.—The factors concerned in the production of total hepatoptosis are discussed in the article on visceroptosis (Vol. III. p. 860), of which ptosis of the liver is but a part; here we have to deal only with the manner in which the prolapsed organ assumes an abnormal degree of mobility. The increased mobility has been ascribed to a congenital elongation or laxity of the ligaments of the liver, but there is absolutely no evidence in favour of this contention. The ligaments, as we have seen, take no part in the suspension or support of the normally placed liver; it is only when the support of its visceral shelf is withdrawn, on account of a lax or weakened action of the abdominal musculature in the upright posture, that the ligaments take a part in the support of the liver and have a continuous strain thrown on them. In the early stages of hepatoptosis the strain is relieved by the descent of the diaphragm, but in the later stages, when further descent of the diaphragm is impossible, owing to its fixation by structures in the thorax, the strain becomes severe, and under its continued action the ligaments become altered in form and elongated. But even in marked cases, such as that reported by Clarke and Dolley, the mesohepar when stretched measured 13 mm. only. In some reported cases the lateral or falciform ligaments were absent (see Binnie, and Terrier), but it is physically impossible that their absence—even if we accept the crude accounts published as correct—could materially influence the mobility of the liver. Graham estimates that in 5 per cent of cases of prolapse of the liver there is a history of a sudden strain or injury.

Incidence as regards Sex, Age, and General Population.—Saweljew has summarised the cases of movable liver reported in medical literature up to 1905: out of 117 cases, 103 were in females (93 married, 10 single), 13 were in males, and 1 in a child. In 30 cases Einhorn found 9 males, Graham 14 in 70, Glénard 11 in 80. The proportion is about 8 women to 1 man. Contrary to what might naturally be expected, it occurs nearly as often in women who have not borne children as in those who have. In 496 autopsies on children Freeman found 4 cases of movable liver, an altogether abnormal proportion. The majority of patients coming for treatment for this condition are between 30 and 50 years of age. Including all conditions of hepatoptosis, Glénard found the condition in 25 per cent of male and 15 per cent of female patients.

Condition found after Death.—After death a liver, which formed a

freely movable tumour in the right loin during life, appears on a superficial examination to occupy almost its normal position. The recumbent posture of the body, the post-mortem distension of the intestine by gas, and the rigidity of the abdominal wall, combined with a certain degree of relaxation of the diaphragm, lead to a reposition of the liver to a varying degree. A closer examination of the abdominal contents will invariably reveal a condition of general visceroptosis: the pylorus is at the level of the umbilicus instead of in the transpyloric plane, the gastro-hepatic omentum is elongated, the hepatic flexure and transverse colon approach the level of the anterior iliac spines, and the domes of the diaphragm are 1 to $1\frac{1}{4}$ in. [25 to 45 mm.] below the level of the sterno-ensiform plane. The liver is either of the dextroverted or anteverted type; almost invariably a constriction or depression traverses it in the line of the waist. In the *anteverted* form the left lateral ligament and extremity of the left lobe are thinned and extended into a vertical fibrous border (see Fig. 3), the liver forming a flat cake-like organ with an irregular lower border. In the *dextroverted* form the liver assumes the shape shewn in Fig. 3. The right lobe is greatly elongated; the left lobe is rotated to the right so as to occupy the right dome of the diaphragm; the mesohepar, on account of the profound changes in the shape of the liver, appears to have a narrow attachment towards the left extremity of the liver, the greater part of the right lobe having no direct attachment to the diaphragm.

Symptoms.—In addition to the multiple symptoms which may be present in visceroptosis, the condition of movable liver has certain peculiar features, the chief being those elicited by a physical examination of the patient. On *palpation* a large, smooth, semi-plastic tumour is felt both in the right loin and extending from the costal margin to the level of a line drawn from the right anterior superior iliac spine to the umbilicus; in the dextroverted form (Fig. 3) the extremity of the tumour may be recognised below that line in the right iliac fossa. The lower margin may also be felt; in the dextroverted form it is vertical in position; in the anteverted form it is irregular in shape, with a deep hepatic notch, and approximately horizontal in position (Fig. 3). The gall-bladder is often palpable, for in nearly half the cases of movable liver it is distended, and projects one to two inches beyond the border of the liver, its fundus usually lying somewhere between the umbilicus and the right anterior superior spine. The liver is felt to be freely movable; it moves with respiration; it may be pushed upwards, unless fixed by pathological adhesions, until a considerable part of it has passed into the right hypochondrium; in 14 out of 80 cases the liver could not be replaced (Glénard); it can be easily displaced towards the left side of the abdomen, but when the pressure is removed it returns to its original position. When the patient stands up the lower border of the tumour may descend two inches or more, and when the patient turns on to the left side, the tumour falls towards that side. On *percussion* the dulness of the tumour is found to be continuous with that of the liver; the upper limits of the absolute dulness and of the deep dulness of the liver are

1 to $1\frac{1}{2}$ in. [25 to 40 mm.] lower than normal, as measured from the sterno-ensiform plane in the right mid-clavicular line. In the dextroverted form the hepatic dulness is greatly diminished or absent in the epigastric region, and in its place there is the tympanitic note of the stomach or colon, which have moved into the space vacated by the liver. On *inspection* the epigastric space is seen to sink in and the hypogastric region to protrude when the patient stands up. The umbilicus is drawn inwards and usually hidden in a transverse fold of the abdominal wall, which is lax and often shews divarication of the recti.

The aching pain felt in the region of the liver or radiating to the back, and not infrequently referred to the right shoulder, the dragging sensation, and vague bodily discomfort disappear when the patient lies down. Sitting up may give rise to such acute distress that physical exertion is impossible. Pressure over the tumour elicits tenderness in only a small percentage of cases. The patient is commonly the prey of those obscure mental symptoms grouped under neurasthenia. According to Dutton Steele acute attacks of colic occur in 84 per cent of cases of movable liver; these attacks, though resembling biliary colic, are not caused by gall-stones, which are present in only one case in five. A slight degree of jaundice is often present (33 per cent, Dutton Steele). The disturbance in the biliary system is probably due to a kinking of the bile-duct, which results from the vertical position and displacement of the liver. The flow of bile from the gall-bladder to the duodenum is obstructed (Dutton Steele). The superficial veins of the abdomen may be enlarged and the feet oedematous, for the dragging of the liver on the diaphragm obstructs the return of blood by the hepatic veins and inferior vena cava. This may also be due in part to a marked change in the mechanism of respiration. The abdomen and lower part of the thorax are almost stationary, the respiratory movements being chiefly performed by the upper part of the thorax. The difficulty in breathing may amount to dyspnoea. A dry cough may be present, and is probably due to irritation of the terminal fibres of the phrenic nerve in the neighbourhood of the mesohepar; the cough usually disappears when the patient lies down. Einhorn classifies cases of movable into five groups according to their symptoms: those with (1) no symptoms; (2) with dyspepsia; (3) with hepatalgia; (4) with biliary colic; (5) with asthma.

Diagnosis.—The condition of movable liver has been mistaken for (1) movable kidney; (2) intermittent hydronephrosis; (3) a Riedel's lobe, but more frequently that condition is mistaken for a movable liver; (4) a greatly distended gall-bladder; (5) cholelithiasis; (6) hydatids of liver; and (7) tumours or cysts of the omentum. In about 20 per cent of cases the right kidney is also freely movable.

Prognosis.—From the scanty records at present available it may be safely inferred that the condition of movable liver, however much it may disturb the health of the patient, does not endanger life. Short of operative treatment alleviation only can be promised. The results of operative treatment are highly favourable.

Treatment.—In every case of movable liver visceroptosis is present, and therefore all general and palliative treatment must be on the lines prescribed for that condition (Vol. III. p. 880). Acute attacks of pain may be relieved by rest in the supine position, the bed being raised so that the hips are maintained on a higher level than the head. Dragging sensations, general bodily discomfort, and obscure pains referred to the region of the liver are always relieved by rest in bed.

The special means at our disposal for the treatment of mobility of the liver are two in number—(1) to afford the abdominal viscera an artificial support by the application of specially designed corsets, bandages, or belts ; (2) if these fail to give relief, operative measures.

Whichever form of mechanical support be chosen—corsets, strappings, or belts—its application requires the utmost care. On the whole, a special form of corset, either of the straight-fronted make or the form designed by Gallant, is the preferable form of support, although various methods of strapping, such as that employed by Kemp (Vol. III. p. 880), and abdominal belts are also much employed. The corsets must be carefully fitted so that, while they are moulded to the region of the iliac crest and hip, they also grip firmly and compress the hollow above the iliac crests. Before applying corsets the patient must assume the supine posture and flex the thighs and knees to relax the abdominal wall. While in this position the liver is pushed upwards and replaced as far as possible, and the corsets applied. They are laced from below upwards, the lacing in the lower half of the corsets being tight, that in the upper half loose. The corsets should be removed only when the patient has again lain down.

Surgical Treatment.—The aim of the surgeon is to replace the liver as far as possible in its normal position, and to produce an adhesion between the anterior surface of the liver and the diaphragm and anterior abdominal wall. This operation, described as hepatopexy, was introduced by Gérard Marchant in 1891, and a full account of the numerous modifications of his operation has been published by Terrier (21). A vertical incision in the right rectus, near its outer border, some 5 or 6 inches in length, or an oblique one parallel to the subcostal margin, gives free access to the liver. In replacing the organ the rotation of the dextroverted form must be undone. A series of double sutures, two to six in number, is inserted transversely in the liver, either through the whole thickness of the lower border or only including a superficial bridge of tissue, on the anterior surface, some $1\frac{1}{2}$ or 2 inches in extent. The sutures are of silk or of catgut, and the series is preferably commenced at the right extremity of the liver. The sutures are then carried into the substance of the diaphragm, anterior abdominal wall, or round the adjacent costal cartilages, tightened and tied. One of the sutures includes the falciform ligament, which is duplicated and included within the suture when tied. To set up an adhesive inflammation, the anterior surface of the liver is scraped (Santucci), or rubbed with an irritant, such as undiluted carbolic acid (Watson Cheyne). The patient is kept in a recumbent position for six weeks after the operation, stays being fitted on

before getting up. It is well to raise the foot of the bed, so that gravity may assist in maintaining the liver in position. In cases in which the abdominal wall is unduly lax Depage excises a vertical ellipse from the median part of the anterior abdominal wall, and brings the edges together so as to form a vertical wound, thus tightening the abdominal parietes. Péan proposed to form a horizontal peritoneal fold on the right side of the abdomen to act as a shelf for the support of the liver. The results of hepatopexy are very favourable : of 18 cases collected by Terrier, 15 were cured, 1 died, and in 2 the result was unknown. Of 2 cases reported by Sir Watson Cheyne, 1 was cured, the other relapsed after six months. Amongst the earliest cases of cure by operative means in England is that reported by Sir F. Treves in 1896, and another by Mr. Ramsay in 1897.

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A. K.

FUNCTIONS OF THE LIVER AND THEIR DISORDERS

By WILLIAM HUNTER, M.D., F.R.C.P.

CONTENTS—

- (1) Nature of Functions ; (2) Manifestations of their Disorders ; (3) Etiological Factors concerned in their Production ; (4) Pathogenesis. (A) Disturbances connected with Proteolysis and Protein Metabolism ; (B) Disturbances connected with Antitoxic and Excretory Functions ; (C) Disturbances connected with Glycogenesis and Carbohydrate Metabolism ; (D) Disturbances connected with Fat Metabolism ; (E) Disturbances connected with Biliary Functions ; (F) Disturbances in Digestion connected with Functional Hepatic Insufficiency.

1. NATURE OF FUNCTIONS.—No organ of the body discharges at one and the same time so many varied and complex functions as the liver. It is the chief assimilative organ, the chief antitoxic and defensive organ, an important organ of excretion, and lastly, through the agency of its biliary secretion it plays an important part in digestion. All these processes are carried out in close connexion with each other ; each of them possesses, nevertheless, a certain independence. The sum total of its various activities is evidenced by certain definite anatomical, chemical, and physiological changes :—(1) The formation and subsequent disappearance of glycogen in connexion with the storage and subsequent disposal of sugar (*glycogenetic and glycolytic function*). (2) The storage and distribution of fat (*fat-storing and fat-splitting functions*). (3) The disintegration of proteins, and the profound modification by oxidative, hydrolytic, synthetic, and other metabolic processes of the various products of protein metabolism—with formation of urea and bile acids and bile pigments as the most obvious end-products (*proteolytic functions*). (4) As the result of these combined processes a remarkable degree of detoxication of the portal blood—which loses the highly toxic properties (*e.g.* in respect of ammonia) it formerly possessed (*detoxicating and defensive functions*). (5) The excretion of bile containing certain of the products of proteolytic metabolism—namely, bile salts and bile pigments (*biliary function*). (6) The action of the bile in the intestine in digestion (*a*) in emulsifying fat, thereby greatly facilitating its ready assimilation ; (*b*) in promoting intestinal peristalsis and in controlling intestinal putrefaction. (7) Lastly, as the result of the extensive combustion processes connected especially with carbohydrate metabolism, the liver is a great producer of animal heat.

These various processes are carried out largely by the aid of appropriate ferment (proteolytic, glycolytic) produced by the liver-cell, and able to produce these effects even after death ; thus, by the process of self-digestion or autolysis, the following products can be formed,—leucine, tyrosine, glycocoll, xanthine bases, ammonia—resembling those resulting from tryptic digestion. These intracellular ferment do not originate in

the digestive canal, and the proteolytic ferment of the liver is not identical with trypsin ; moreover, it is particularly active, destroying proteoses with much more vigour than does the enzyme concerned in autolysis of the lung. These ferment activities differ from those exercised by other digestive glands, such as the stomach, intestine, and pancreas, inasmuch as the proteolysis and glycolysis they effect take place within the liver-cell—not in cavities such as the stomach and intestine into which the ferments are poured. This peculiarity exposes the liver-cell in a special degree to disturbance, to the extent even, in the case of severe toxic influences, of contributing to its autolysis when it is left exposed to the action of its intracellular proteolytic enzymes unchecked by the influences which normally control their activity. The conditions presented by the liver in acute yellow atrophy, chloroform and phosphorus poisoning exemplify the powerful destructive action of the proteolytic enzymes present in the liver-cell. Lastly, the manner in which the liver-cell disposes of the products of its various activities calls for notice ; whilst most of them are returned into the blood, others are no less invariably excreted into the bile-capillaries and thence along a long system of bile-ducts lined with a mucus-secreting epithelium. Since the bile is secreted at a low pressure and is liable to contain irritant products capable of causing catarrh, a fresh element of disturbance is introduced. For the catarrh so caused is apt to retard or even to obstruct the flow of the bile completely, disturbing not only the biliary functions (biliousness, jaundice, and cholelithiasis) but also the other functions of the liver-cells.

2. MANIFESTATIONS OF FUNCTIONAL DISTURBANCES OF THE LIVER.

—The above summary of its functions may indicate the numerous directions in which the liver-cell is open to functional disturbance which must affect the character of the blood and, indeed, of nutrition generally. As every disturbance of the activity of the cells influences the proper performance of other functions, a number of phenomena are combined in the symptom-group of hepatic insufficiency. According to popular belief, based largely on Murchison's teaching, the symptoms of hepatic inefficiency extend to the most diverse parts of the bodily economy.

Arranged under the systems with which they are connected these symptoms and manifestations are the following :—

(1) *Alimentary System*.—Mouth and Tongue : loss of appetite, furred tongue, bitter taste in mouth, variable or perverted appetite ; in severe toxic cases dry tongue. Stomach and intestine : a sense of weight and fulness in the epigastrium, heart-burn and acid eructations, nausea, flatulence, vomiting, mucous colic ; in toxic cases, haematemesis. Constipation with scybala motions, sometimes dark, and at others clay-coloured, or diarrhoea with bilious stools. Liver : sallowness of complexion, biliousness, conjunctival jaundice, pale or bilious stools. Definite jaundice ; sense of fulness and weight over liver. "Chill on the liver" ; also structural changes, for example : congestion of the liver, fatty change, cholelithiasis, cirrhosis, acute yellow atrophy.

(2) *Cardio-vascular.*—Palpitation, pulse slow or irregular and intermittent, and in severe toxic conditions such as cirrhosis, and acute yellow atrophy, very rapid ; arterial changes, fatty, fibroid, and calcareous, met with in old age, or in gouty subjects.

(3) *Renal.*—High-coloured urine, with deposit of lithates or uric acid, urinary calculi, oxaluria, and many other changes in the characters and proportions of the urinary constituents, such as ammonia, acetone, oxybutyric acid, leucine, tyrosine, aromatic sulphates, functional albuminuria, glycosuria ; as structural changes, chronic degenerations, for example the gouty kidney ; gouty deposits.

(4) *Nervous.*—A very large and prominent group of symptoms ; frontal headache, langour and disinclination for work, drowsiness after meals, irritability of temper, dulness and heaviness, great depression of spirits amounting in some cases to melancholia, sense of oppression and weariness, wakefulness at nights, bad dreams, attacks of vertigo or dimness of sight ; in severe cases still more striking nervous and mental effects of cholaemia, delirium, coma, acute maniacal disturbance.

(5) *Integumentary.*—In a certain class of cases—acute rashes, erythematous or urticarial ; or more chronic conditions, such as acne, lichen, or chronic erythema, pigmentation, xanthelasma, lupus erythematosus, furuncles, diabetic gangrene.

(6) *Ligamentous, Cartilaginous, and Osseous Systems.*—In some cases—chronic rheumatic affections ; more commonly gouty inflammations and deposits.

The liability to these diverse disturbances is, it is alleged, associated with a particular temperament, the so-called bilious constitution. Its manifestations include a sallow complexion, a dark oily skin, irregularity of features ; general inefficiency of the alimentary system, marked more especially by a deficient or by excessive secretion of bile, and great liability to alimentary disorders ; and certain peculiarities of cerebral and mental functions, to wit—a staid and melancholic character usually marked by great irritability of temper,—often associated, it is conceded, with possession of powerful intellect.

Tinged as it may be by some degree of exaggeration, this general belief nevertheless accurately represents the wide range and general importance of the class of disturbances which may in individual cases be the outcome of the functional derangements of the liver. The information gained since this conception was propounded by Murchison in 1874, while necessitating some modification as regards particular points, has at the same time only served to emphasise the general importance of hepatic disturbances in relation to general health. It has brought out more particularly the extraordinary part taken by the liver as the greatest defensive organ of the body ; it has revealed to us in more detail the numerous weapons it employs in discharging its various functions, and its extraordinary adaptability in meeting the excessive claims constantly made upon it to a degree unknown in the case of any other organ of the body. But for this adaptability the number of disorders connected with it would

be even more numerous and severe than they are ; for blameworthy as the liver often is, and in popular estimation it is held to be so still more, in many cases it is without doubt the most "abused" organ in the body, alike in opinion of the sufferers and in actual functional experience. In a large number of disorders assigned to it, it is as much the sufferer as the cause of suffering.

3. THE ETIOLOGICAL FACTORS concerned in the production of functional disturbances of the liver may be grouped as follows :—

(i.) *Physiological and anatomical factors* connected with (a) the multiplicity of its functions, (b) its biliary structure, and (c) its relations to the portal circulation on the one hand and to the right side of the heart on the other, which expose it in a special degree to congestions, active or passive (p. 155).

(ii.) *Digestive Disturbances*.—This heading includes more particularly all the manifold disturbances of gastro-intestinal digestion arising from (a) diminished, increased, or perverted action of the digestive secretions (salivary, gastric, biliary, pancreatic, intestinal) poured into that tract, apart altogether from any error in the amount of food taken, but greatly increased by excess of food ; and (b) disturbances in the functional activity of the mass of lymphoid cells in the mucosa, which determine in a special degree the formation of uric acid and the variations in its excretion so commonly met with in digestive disorders.

This factor is a common and a most important one ; a large proportion of the symptoms connected with the alimentary tract, popularly regarded as those of "liver disturbance," such as coated tongue, feelings of weight and fulness, constipation, uric acid excretion (*vide* p. 36), are symptoms of the digestive disorders causing the liver disturbance, not of hepatic disorder.

(iii.) *Errors in Feeding, and especially Over-feeding*.—This is the most important factor of all in health, both in causing the digestive disturbances just referred to, and in throwing increased metabolic work on the liver itself, thus affecting all its functional activities.

(iv.) *Under-feeding or inanition* in comparison affect the liver function but little, at least in health. They only do so when associated with or dependent upon disease of the liver itself, such as fatty metamorphosis, congestion, cirrhosis, or jaundice. The lowered proteolytic and glyco-genetic metabolism associated with the under-feeding and inanition of such conditions, whilst not a source of any serious disturbance by itself, may become a source of the gravest trouble, if the liver become at the same time exposed to additional disturbance from the action of toxic agents. In such circumstances, as exemplified by the last stages of cirrhosis, severe toxic jaundice, acute yellow atrophy, chloroform poisoning, phosphorus poisoning, the functional activity in nutrition may become so reduced as to endanger the structure of the liver-cell. The liver-cell becomes exposed to the destructive action of its own proteolytic ferment—a process of self-digestion or autolysis may set in, either in the parts

of the liver affected, for example in cirrhosis, or in the whole liver, as in acute yellow atrophy, and result in the complete disintegration of the liver-cell with suppression of all its functions, not only the proteolytic and glycogenetic, but still more of its antitoxic functions. The disturbances then brought about are among the most severe, violent, and fatal known to the body (cholaemia or hepatic toxæmia).

(v.) *Gastro-intestinal Intoxication.*—This constitutes the most common and fertile source of hepatic disturbance, both functional and organic. The toxic products may have a double source : (a) from the food, by the action of the enzymes of the digestive juices (digestive toxins); or (b) from the food products, by the action of the bacteria of the intestine (bacterial toxins). The latter may again be divided into two groups : (1) those due to the action of the bacteria normally present in the digestive tract ; (2) those due to specific pathogenetic organisms either constantly present and under suitable conditions greatly increased in numbers (*e.g.* streptococci or staphylococci, *B. lacticus* or *B. butyricus*) ; or introduced into the intestine by definite infection, for example, enteric fever, dysentery, tuberculosis, or special icterogenous infections, such as those of yellow fever, Weil's disease and other forms of febrile toxic jaundice. The disturbances induced by these toxic factors affect every function of the liver-cell. The character and intensity of these disturbances differ, however, materially in different individuals, and in the case of the different toxic products ; these differences are largely determined by the effect produced on the appetite, and consequently on the general nutrition of the individual.

When the appetite remains good, or is even in excess, as is the case in the "good liver," the amount of extra work which the liver can perform in dealing with the excess of digestive and bacterial toxic products thrown upon it is, as daily experience shews, enormous. The general effect is corpulence, arising from the storage of fat introduced with the food or formed from the carbohydrates of the food. The special disturbances arise in connexion with the disposal of the toxic products, derived in excess from the albumin in the food. They are definitely toxic (*for example*, ammonia) even in health ; in many cases, as shewn by the conditions of catarrh which their presence induces in the gastro-intestinal tract, they are oftentimes definitely irritant. The passage of such products in increased quantity to the liver throws a greatly increased work on the metabolic, antitoxic, and biliary functions of the liver-cell. When these are overtaxed, the products pass through the liver-cell unchanged into the general circulation on the one side, or the bile passages on the other, causing general toxic symptoms in the one case, such as headache, giddiness, irritability, depression, or exciting some degree of biliary catarrh on the other, *for example*, biliousness.

If, on the other hand, the appetite be impaired, and the intake of food be materially lessened (as in prolonged gastro-intestinal intoxication, arising from digestive disturbances, excessive putrefactive decomposition, and excessive use of alcohol), the disturbances induced by the continuous

absorption of toxic products are of a much more marked character. They may extend to the liver structure itself, and the general disturbances mentioned above become more or less chronic; the individual becomes then the "livery subject," and in addition there is liability to degenerative (fatty), congestive (chronic engorgement of the liver), and inflammatory disorders in the liver (hepatitis and cirrhosis). The continued excretion of irritant products in the bile, by maintaining more or less catarrh of the bile passages and of the gall-bladder, leads to the increased formation of cholesterin, and to cholelithiasis, and thus directly and indirectly to the numerous complications connected with the presence of gall-stones.

(vi.) *Fever and general infections* necessarily modify the functional activity of the liver; in most cases this is in virtue of their effect on the appetite, and consequently on the intake of food. In all cases, however, fever is accompanied by increased nitrogenous metabolism (proteolysis), and consequently by increased work to the liver (in urea formation). It is also marked by diminished glycogenesis and secretion of bile. In most cases this effect is due to the action of the toxin rather than of the fever. To what extent the effect is due to a toxic destruction of protein, apart from its effect on diet, is debatable. Pyrexia, *per se*, causes but little protein disintegration, and clinically the wasting is by no means directly proportionate to the amount of fever, but depends largely on the character and intensity of the infection. So far as the liver is concerned, the effect of infection is in general intensified when the infection is gastro-intestinal in origin. But the degree of disturbance caused is determined more by the character of the poison than by the site of infection, or by its effect on nutrition, or by the degree of fever. The clear eye and unclouded intellect of the consumptive patient, in spite of many weeks of hectic fever, denote that fever and infection *per se*, however much they may affect nutrition, do not necessarily cause any special form of hepatic disturbance. The absence of liver disorder in such cases contrasts with the severe constitutional disturbances and jaundice which mark the various infections underlying Weil's disease and other forms of toxæmic jaundice.

(vii.) *Blood diseases* affect the liver in some cases. The result is determined by the character of the toxin occasioning the blood change, or the products formed by their action, for example haemoglobin in pernicious haemolytic anaemia, uric acid in leukaemia and splenic diseases. The greatest degree of disturbance is associated with the action of haemolytic poisons. The special manifestations of this disturbance include (a) an increased formation of bile pigments—a polychromia with consequent urobilinuria as the result of the increased amount of haemoglobin set free, chiefly in the intestinal capillaries and the spleen; (b) a diminished formation of bile acids; (c) varying degrees of jaundice from the slightest to the most severe, due to catarrh set up by the excretion of the irritant toxins in the bile (Hunter); (d) functional changes affecting proteolysis, glycogenesis and fat metabolism, and detoxication; and (e) in some cases,

e.g. pernicious anaemia, leukaemia, structural lesions in the liver-cell, namely, fatty change and deposition of blood pigment.

(viii.) *The Influence of the Nervous System.*—The nervous system exercises a definite control over the functional activity of the liver, not only indirectly by determining the amount of blood in the portal system, but also directly through the influence of mental emotion on the liver-cell itself. The "attack of liver" which in common experience may be brought on by worry and anxiety need not necessarily be wholly due to any disturbance of digestion created. The control of the sympathetic nervous system on the functions of the liver is more direct, as shewn by Claude Bernard in the production of glycosuria by puncture of the floor of the fourth ventricle, and by glycosuria in some cerebral diseases. In disease, it is true, this influence is ill-defined; but its existence must not on this account be set aside as negligible. As will be afterwards seen, it has been held to play an important part in the production of the severest forms of liver disturbance, to the extent even of bringing about "suppression" of its functions. It has been thought to explain emotional jaundice (p. 93) and to cause entire arrest of hepatic functions, for example in acute yellow atrophy. This belief in the possible effect of mental emotion on liver metabolism, based on clinical experience, receives some support from recent pathological observations regarding the part played by autolysis or self-digestion in liver disease. If the intracellular alkalinity in the liver-cell fall to a low point, as the result of the acidosis of inanition or previous liver disease, the effect of severe mental depression or emotion accompanying severe liver disease or preceding operations, may well be, in particular cases, to depress the functional activity of the liver-cell beyond the point at which it can resist its own proteolytic ferments. When once these have gained the mastery, the course taken is the fulminating one presented by cases of acute yellow atrophy occurring either independently or following the post-operative vomiting of chloroform poisoning.

(ix.) *Functional Disturbances and Diseases of other Organs.*—There remain to be noted the possible effects on the liver of disturbances and diseases of other organs. The activity of the liver is affected by disturbances in other organs, notably of the pancreas (in diabetes), adrenals (in glycosuria), thyroid, and kidneys. The internal secretions of the pancreas, adrenals, and thyroid influence in a special manner the glycolytic function of the liver and incidence of glycosuria (see p. 44). The functional activity of the kidney in excretion by materially affecting the character of the blood must in many cases affect that of the liver. But this effect is far less than what might, a priori, have been expected—in itself a proof of the general adequacy of the liver activity, even in severest diseases. For most, if not all, of the products of metabolism dealt with by the kidney have already been dealt with by the liver before they reach the general circulation, and have been deprived of any toxic properties they may have. If returned again to the liver, as they must be, in nephritis, their effect on the liver is but slight.

Liver disturbance is in consequence not a special feature of even the severest forms of Bright's disease. On the contrary, kidney disturbance is more apt to be the result than the cause of hepatic disturbance.

4. PATHOGENESIS.—This subject will be considered under the following headings: (A) Disturbances connected with proteolysis and protein metabolism; (B) Disturbances connected with the antitoxic and excretory functions; (C) Disturbances connected with glycogenesis and carbohydrate metabolism; (D) Disturbances connected with fat metabolism; (E) Disturbances connected with biliary functions; (F) Disturbances in digestion connected with functional hepatic insufficiency.

A. **Disturbances connected with Proteolysis.**—The task of dealing with the numerous and varied products of digestive proteolysis falls chiefly on the liver, and it is in connexion with its functions in this relation that its chief disturbances arise, both in health and disease. These disturbances manifest themselves in three directions: (a) by urinary changes; (b) by various toxic symptoms due to insufficient detoxication of the portal blood. These are mainly nervous, varying from headache, giddiness, drowsiness, irritability, up to the most severe phenomena, marked by vomiting, delirium and coma; but in some cases they take the form of rashes; (c) by biliary disturbances, connected with the quantity and quality of the bile excreted, and conditions of catarrh in the bile passages set up by the excretion of irritant products in the bile.

In all cases these disturbances are accompanied by various nutritional disturbances affecting the body as a whole (emaciation or corpulence), or particular systems of it, for example, the joints in gout, arterial degeneration, the kidneys. In many cases they are also accompanied by definite structural lesions of the liver, e.g. fatty change in the cells, in connexion with the vessels, e.g. acute or chronic congestion; or in the interstitial tissue, e.g. cirrhosis due to the excretion of toxic products. The chronic inflammatory changes of a non-infective character thus produced are only paralleled by those found in the kidney. Lastly, functional disturbances in proteolysis may in certain cases be manifested by self-digestion or autolysis of the liver-cells (*vide p. 23*).

1. *Quantitative Changes in Nitrogenous Excretion as Evidence of Functional Disturbance of the Liver.*—The nitrogenous changes of special importance in connexion with disturbance of the proteolytic function of the liver are the excretion in the urine of (1) the total nitrogen; (2) urea; (3) ammonia; (4) amido acids, e.g. leucine and tyrosine; (5) uric acid; (6) oxalic acid; and (7) the excretion in the bile of bile acids and bile pigments.

(a) *The Effects of Diminished Nitrogenous Metabolism.*—The total nitrogenous excretion in health averages from 10 to 16 grams, and is made up chiefly of urea to the extent of 90 per cent and ammonia 3·5 per cent. The variations met with in disease, apart altogether from anomalies of excretion in kidney disease, depend largely

on the intake of food and the degree of fever, and by themselves throw little light on the functional activity of the liver.

In starvation the total nitrogenous excretion may fall as low as 3 grams, in some cases below even 2 grams. In chronic malnutrition it is also low—5-6 grams. In both cases the result depends largely on the previous health. In starvation the organism first economises its own protein by the combustion of its reserves of fat. Hence underfed persons become poor in fat, poor in muscle, poor in strength, and this loss of body protein cannot be prevented by a large diet of protein alone unless supplemented by carbohydrates and fat. So far as the liver is concerned, the effect of malnutrition must be to diminish its work in relation to the proteolysis of food products. This is evidenced not only by diminished nitrogenous excretion, but also by diminished secretion of bile (by one-half, two-thirds, or in some cases even three-fourths), by its increased concentration, and by reduction in the amount of its pigments and acids. Its work in relation to tissue proteolysis, especially that of muscle, is, however, increased. Its own tissue shares in this increase, a point of importance in connexion with some of the disturbances to which it is liable. In long abstinence from food, or in conditions, such as cirrhosis of the liver, in which the food supply is insufficient or does not reach the liver, the intracellular alkalinity may be unduly reduced, and the liver-cell be in consequence exposed unduly to the action of its (acid-forming) proteolytic ferments, with danger to its own stability and structure. In such circumstances if the structural and functional stability of the liver be further reduced by additional pathological factors, such as actual toxic factors or profound emotional disturbances, there is an exceptional liability to profound disturbance. Its own proteolytic processes may gain the mastery of it, the result being autolysis or its own destruction.

Effects of Reduced Proteolysis on Glycogenetic and Fat-Storing Functions.—The glycogen is consumed rapidly at first, but more slowly afterwards. Even in advanced degrees of starvation the liver usually contains a small amount of glycogen. But in certain circumstances there may be a very considerable amount—formed either from the carbohydrate moiety of the protein molecule or from carbohydrate. The glycogenetic and glycolytic activities of the liver are thus of a very stable character, even in starvation and malnutrition. They are only affected quantitatively. Thus, the “assimilation limit” of the liver for sugar is not materially lowered (von Noorden). In health the limit for glucose is 200 grams, and in starvation 100-150 grams (*vide p. 45*). But the diminished glycogenesis, whether arising from lessened power, or from want of sufficient carbohydrate in the food, carries with it other ill effects. It lessens heat production, so that the poorly nourished individual is also a cold one. In this way it tends indirectly to further tissue proteolysis; the body endeavours to compensate the loss of heat by increased combustion of the protein of its tissues in place of the simpler and easier process in health, viz. combustion of the carbohydrates of the food; and by increased combustion of the fat of its tissues.

The effect of starvation, including reduced proteolysis, in increasing fat metabolism, is considered on p. 49. The point which concerns us at present is, how far this fat storage in the liver influences the proteolytic function of the liver-cell, as judged by its total nitrogenous metabolism. A priori we should anticipate that the effect would be considerable, since excessive storage of fat in the liver-cell should interfere greatly with its proteolytic metabolism. This, however, is not the case to any appreciable extent, and even under the most unfavourable conditions, to wit, extensive fatty change, the excretion of nitrogen and of urea may not only be undiminished but absolutely increased. Thus, in a case observed by von Noorden, a woman with phosphorus poisoning while absorbing practically no food, excreted an average of over 15 grams of nitrogen from the second to the sixth day, and an average of over 14 grams from the seventh to the eleventh day. As will presently be seen, severe conditions of fatty change in the liver produced by toxic agents are accompanied by evidence of some qualitative disturbance in the liver functions in relation to the nitrogenous metabolism. The normal proportion of urea (90 per cent) to the other nitrogenous constituents of the urine is diminished. But the important point is that even in these adverse circumstances the total urea formed approximates the average in health on a normal diet, and largely exceeds the amount which would be formed by the liver under similar conditions of feeding. Even in cases of extreme fatty change the proteolytic functions of the liver are thus largely retained. The same holds true of the other condition of the liver, cirrhosis, characterised not only by fatty change in the liver-cells but by a great reduction of their number. The lessened nitrogenous excretion which may be met in some (not all) cases of this disease, is the result of the diminished intake of food and of the escape of urea into the ascitic transudations. The general belief that the low urea values found in such cases necessarily denote disturbance of the urea-forming function of the liver is not justified. The reason for the low values found in such cases is connected with the protracted state of inanition of the patient. They are not unfrequently accompanied by diminished excretion of sodium chloride, a sure sign of inanition. Lastly, the striking recovery that sometimes immediately follows the Talma-Morison operation or the establishment of a collateral circulation, shews that the liver functions, however impaired by the preceding inanition and toxæmia, have not been materially affected.

There remains to be considered the effect of jaundice in its various forms, both simple and toxæmic, on the proteolytic functions of the liver. Jaundice is often marked by a poor state of nutrition; this is due partly to the poor absorption of fat, partly to the loss of appetite, partly to the digestive disorders which so often are its cause or are its result. Hence in jaundice a call is commonly made on the patient's tissue protein and fat. In addition, the stagnation of bile must interfere with the functions of the liver-cell; estimations shew, however, that this interference does not specially affect the total nitrogenous metabolism. This may remain at 10, 15, or 17 grams per day (normal = 16 grams); even in

jaundice due to malignant disease accompanied by intense cachexia values of 9 to 11 grams were found by von Noorden. In general it may be said that the loss of nitrogen is greater than would be expected in absolute inanition, and hence that proteolysis is relatively increased rather than diminished in simple jaundice of long standing.

Apart from nitrogenous excretion in the urine proteolytic activity is evidenced by the excretion of bile pigments. In simple obstructive jaundice these continue to be freely formed, shewing that that portion of proteolysis concerned with the destruction of haemoglobin is not materially impaired. Moreover, this holds good even in toxæmic jaundice in which toxins, as well as bile stasis, act on the liver-cells. In most of these conditions, the formation of bile pigment is increased. Their chief feature indeed is an increase of bile pigments or polychromia (see p. 55).

The opposite condition of acholia has been often assumed to exist in connexion with biliary stasis, and presumably as its result. It has been held to denote that the biliary function of the liver may be suppressed, while the other functions are retained. As will be afterwards seen (p. 84) there is no conclusive evidence of this. The acholia observed in such conditions has been specially noted in diffuse tuberculous disease of the liver, in fatty liver, and in many forms of cirrhosis. It is stated to be marked by colourless faeces in patients without any jaundice. In many cases it is probably accounted for by the presence of fat or by infiltration of the faeces with gas.

Another evidence of functional activity of the liver in proteolysis is the formation of bile acids, which are formed by the liver exclusively. The amount present in the urine in biliary stagnation is not great (about 0·34 gram per diem), and as a rule traces only are present. If the amount of bile acids formed in jaundice remained the same (10 grams per diem) as in health, they must either be utilised in metabolism or accumulate in the blood and tissues. There is no evidence of the latter, bile acids injected into the blood being excreted in the bile (Stadelmann). The probable explanation of the small amount of bile acids in the urine in jaundice is that the circulation of bile acids in the portal blood is interrupted after the first few days, and their formation is consequently much diminished. But this explanation cannot apply to those cases of jaundice in which the formation of bile is greatly increased, and nevertheless the production of bile acids is markedly diminished. Hence it appears that the liver-cell is functionally damaged by the action of the haemolytic toxin liberating the haemoglobin, and is no longer able to produce the bile acids although the material for this synthesis is not lacking. This is borne out by analyses of bile from biliary fistulas, which shew that the bile contains 0·2 per cent instead of the normal 2 per cent of bile acids (Yeo and Herroun).

(b) *The Effects of Increased Nitrogenous Metabolism.*—1. The effects of over-feeding on body weight and heat production.—The effects vary according to the nature of the food taken. Over-feeding denotes the administration of food in such a quantity as to provide more energy than the needs

of the body require. According to von Noorden (1893), the store of energy represented by the excess of food over body requirements, with the exception of about 6 or 7 per cent spent on the increased work of digestion, takes the form of an addition to the body substances ; and no further increase in heat production is brought about by such over-feeding. This is certainly true as regards fats, 97-98 per cent of fat in excess being utilised in increasing the body weight. In the case of an excess of carbohydrates the circumstances are different ; probably some 10 per cent of the energy they represent is used up for purposes of their digestion ; and their conversion into fat involves some further loss of energy due to heat production. The result is that the increase in fat is about 30-35 per cent less than what might be expected. In the case of an excess of protein foods, the results again differ. Oxidation processes are increased far in excess of what is required for digestive purposes. The transformation of energy exceeds (by 30 or 40 per cent or more) that which is necessary for maintenance (Rubner, 1903). Excess of fat in the diet thus leads to accumulation of material which adds to the weight of the body, but contributes little to the energy exchange. Excess of carbohydrates gives rise to energy, and leads to the deposition of fat. Excess of albumin involves increase of oxidation processes. But these are spent on its own combustion, and hence very little of the surplus energy is left at the disposal of the body.

The importance of these conclusions is that the quantity of tissue protoplasm and disintegration of protoplasm is determined by the exchanges in energy. Both fat and carbohydrates thus spare protein disintegration, fat being less effective than carbohydrates. The result of this is that an increased retention of the nitrogen of the food and of the tissues can be effected both by excess of fats and carbohydrates, and by excess of albumin. The daily retention of nitrogen which may thus be brought about by over-feeding is as much as 3 to 5 grams of nitrogen. With excess of protein alone the retention is much less, $\frac{1}{2}$ to 2 grams. This nitrogen gain is absolutely, as well as relatively to the simultaneous formation of fat, greatest in those convalescing from severe acute diseases ; it is less, but still considerable, in patients previously in a state of inanition ; it is least in those who are already well nourished. The protein thus compulsorily saved by over-feeding does not remain in the blood and lymph, but is deposited in the cells as "reserve stock"—analogous to the excess of glycogen or fat in cells (von Noorden).

2. The effect of over-feeding on the functions of the liver.—But, as just seen, the amount thus stored up is small in proportion to that broken up by oxidation and other processes. The increased proteolysis thus necessitated by over-feeding must involve a corresponding increase in the number and forms of the by-products of protein metabolism. It must also involve a great increase of the oxidation processes necessary to effect this disintegration, with a corresponding diminution of these processes available for other purposes such as the ultimate disposal (by oxidation) of the products split off from protein in the first instance.

Among these products are many more or less toxic; and others, such as uric acid, chiefly formed by the activity of the lymphoid cells in the gastro-intestinal mucosa, and capable of being split up by oxidation into urea and oxalic acid. A particular set of liver disturbances is thus associated with excess of meat diet, namely (1) diminished detoxication with all sorts of general symptoms (*vide p. 40*) as its manifestations; (2) diminished destruction of uric acid with increased excretion in the urine (lithuria), or with increased retention in the body (uric acid diathesis, gout). The last-mentioned (uric acid) manifestations of hepatic inadequacy are not necessarily confined to large feeders. They may also be found in spare eaters, who appear to be unable to deal with the uric acid derived from the moderate amount of uric-acid-forming substances (purine bases) in a normal diet. To what extent this may be due to (1) increased or perverted activity of the mass of lymphoid cells, in the gastro-intestinal mucosa and elsewhere, by whose agency these purine substances are chiefly broken up, or (2) to inadequacy of the liver in dealing with the uric acid so formed, is not clear. But our knowledge that in certain animals, for example, birds, uric acid takes the place of the urea of mammals, and that in them the liver is as important in the formation of uric acid as it is for the formation of urea in mammals, undoubtedly suggests that in man also the liver is concerned with the metabolism of uric acid, and that disturbances in the formation, excretion, and retention of uric acid may denote hepatic inadequacy. The teaching of Murchison, who considered that "lithuria" was as important a manifestation of hepatic disturbance as glycosuria, thus receives, if not the entire confirmation which he claimed for it, strong support from comparative physiology as well as from actual clinical experience. But this conclusion does not necessarily involve the further one frequently attached to it by certain observers who assert that the symptoms are due to the uric acid itself, and that uricaemia is the essential cause of the various effects which may be associated with it (*vide p. 36*).

Qualitative Changes in Nitrogenous Excretion as an Evidence of Functional Liver Disturbance.—Interesting as the foregoing evidences of the liver disturbance manifested by and associated with quantitative variations in the excretion of nitrogen may be, of still greater interest and importance are the evidences of such disturbance afforded by the qualitative changes, namely, the relative amounts and proportions of the various nitrogenous products excreted in the urine—urea, ammonia, uric acid, oxalic acid, and in rarer cases the amido acids leucine and tyrosine.

Urea. Ammonia.—So far as disturbance of liver function is concerned, chief importance attaches to the proportions of urea and ammonia present in the urine. Urea is normally formed by the liver—chiefly from ammonia carried to it in the portal blood from the intestinal tract; to a certain extent also from protein, intermediate products such as leucine and glycocoll, and probably also by decomposition of the purine bases or uric acid. Variations in the proportions of these substances in

the urine, especially of urea and ammonia, may therefore denote functional inadequacy of the liver. Thus, in acute yellow atrophy of the liver, and in other acute and chronic lesions of the liver, not only is the total excretion of urea greatly lessened, but its place is largely taken by ammonia and intermediate nitrogenous products, such as leucine and tyrosine. The total amount of urea may be so reduced that it can only be detected in traces. Instead of the average 10 grams in starvation, 20 grams on a low diet, and 30 to 40 grams on a full diet, figures as low as 0·4, 0·2, 3·5, 7·2, and 9·6 grams have been found. Of still more interest, however, is the disturbance in the ratio of urea to other nitrogenous products, especially to ammonia. Instead of the normal 90 per cent, the urea may only constitute 81, 79, 75, 71, or 52 per cent of the total. At the same time the percentage of ammonia may rise from the normal (3 to 5 per cent) to over 4, 9, 12, 16, 18, or even as high as 37 per cent. Taken by itself, this increase of ammonia might be held to denote great functional inadequacy of the liver, rendering it unable to transform ammonia into urea. But this increase in ammonia is not necessarily or exclusively the result of inactivity of the liver. For the increased percentage of ammonia may depend on the ammonia having formed some combination, for example, with acids, before reaching the liver, which prevents its conversion into urea, and thus leads to its appearance unchanged in the urine. There is evidence that this is the case, and that in acute yellow atrophy, and other conditions (*e.g.* diabetes) in which the percentage of ammonia in the urine is increased, organic acids are formed in increased quantity. Thus, sarcolactic and fatty acids are found in acute yellow atrophy and phosphorus poisoning; acetone, diacetic, and β -oxybutyric acid in diabetes. The increased excretion and proportion of ammonia with corresponding diminution in the amount and proportion of urea may thus be due to the "acidosis," and not to inactivity of liver function. Conclusive evidence of this is afforded by Münzer's work (1893) on phosphorus poisoning. He found that the increased excretion of ammonia (10-18 per cent) present in cases of acute phosphorus poisoning is due to acid formation—not to functional inactivity of the liver, for it could be quickly diminished by administration of large doses (6 grams daily) of bicarbonate of sodium, a fall from over 16 per cent to 6 per cent being thus effected by the second day. Even though increased excretion of ammonia does not of itself denote hepatic inadequacy, but merely increased acidosis, its significance in relation to liver disturbance still remains. For it is especially with severe disturbances of liver function (diabetes, acute yellow atrophy, cirrhosis) that this acidosis and increased excretion of ammonia are found; there is always the possibility that the acidosis may be due to increased formation of acids in the liver, from the proteins of its own substance in acute yellow atrophy and from the fats in diabetes. Apart from these possibilities, then, combination of ammonia with the organic acids and its passage through the liver unchanged involve possibilities of severe disturbance of liver function.

For in order to maintain nitrogenous equilibrium in the liver-cell, the nitrogenous food-stuffs must be digested in such quantities and in such form that the ammonia produced in the digestive tract is sufficient to maintain the intracellular alkalinity of the liver-cell. In health there is always the excess of ammonia, but it is lower on vegetable than on animal food. The presence of the small quantity normally found in the urine (0·6 to 1 gram daily) is due to its combination with mineral acids set free in the body. After administration of large quantities of hydrochloric acid it is largely increased, three-fourths of the hydrochloric acid reappearing in the urine combined with ammonia. The administration of organic acids, on the other hand, leads to no increase of ammonia, because they undergo direct combustion in the body to form carbonic acid. The organic acids formed in the body (acetone, diacetic, β -oxybutyric acid) do not undergo combustion, but behave like mineral acids, combining with ammonia to form neutral salts. Such acids may be formed in considerable amount in the normal body when carbohydrates are totally withheld, and a purely flesh and fat diet is given. In diabetes large quantities of diacetic and β -oxybutyric acids may be excreted, and the amount of ammonia may rise up to 2 or even 10 grams in the twenty-four hours, and may constitute as much as 25 to 40 per cent of the total nitrogen. Alkalies, conversely, lead to a diminution, and to that extent influence the urea-forming function of the liver. Thus, 12 grams of bicarbonate of sodium lead to a diminution of the ammonia excretion by two-thirds. Similarly the increased acidosis and ammonia excretion, due to a purely meat diet, can be reduced to a fourth by giving 20 grams of bicarbonate of sodium daily for several days—a point of importance to meat eaters.

These variations in acidosis and consequent ammonia excretion must to a certain degree influence the work of the liver in urea formation. But so long as the amount of uncombined ammonia reaching the liver is sufficiently great, as represented by its total excretion of urea, variations in the relative proportions of ammonia converted into urea or excreted respectively need not cause any special disturbance. The position, however, is different when acidosis is associated with either diminished intake of food or inability, from vomiting, to retain food, or with diminution of the liver substance as in cirrhosis. The amount of ammonia reaching the liver may then be so absolutely reduced that the intracellular alkalinity of the liver-cell necessary to maintain its nitrogenous equilibrium is unduly reduced. There then arise the profound disturbances so commonly associated with the later stages of cirrhosis—not only the urinary changes above referred to, such as diminished proportion of urea, increase of ammonia, presence of leucine and tyrosine, denoting disturbance of proteolysis, but also, and far more striking, the toxic symptoms of vomiting, drowsiness, delirium, and finally coma denoting profound disturbance of its antitoxic functions. Lastly, in fortunately rare cases, the alkalinity of the cell may fall even below the point necessary to keep its own acid proteolytic ferments in check.

The liver-cell then digests itself, and the case presents the fulminating toxic features of acute yellow atrophy.

Uric Acid.—The metabolism and excretion of uric acid are largely independent of the ordinary nitrogenous economy, and follow laws of their own. It arises from the oxidation of the nuclein bodies of the food and those of the body, and also partly from preformed nuclein bases such as xanthine, guanine, adenine, hypoxanthine (the xanthine or purine bases). Organic extracts of the liver, spleen, and other organs are able to oxidise these bases into uric acid, and a similar conversion is effected in the living body. Uric acid is formed from them only, and not from the disintegration of simple albuminous bodies; however greatly the nitrogenous metabolism is increased by such albumin, the amount of uric acid excreted is not affected. The old belief that there must be a relation between the total nitrogen and the uric acid excreted therefore no longer holds good, and the quotient can fluctuate from 1:25 to as low as 1:125. Diet is the factor of chief importance influencing the excretion of uric acid (exogenous origin of uric acid). Uric acid of exogenous origin is higher on a meat diet, which contains much nuclein, than on a vegetable diet, since vegetable foods, with the exception of pulses (Walker Hall), contain but small amounts of purine bodies. These latter are also present in beer and porter. Endogenous uric acid is derived from the nuclein bodies of the tissues, and also from free purine bases present in the muscles. It does not cease even after thirty days' abstinence from food, although it falls rapidly after food is withheld. The amount may be determined by feeding on a milk and vegetable diet poor in purines. Investigations carried out on these lines (Burian and Walker Hall, 1903) have led to the important conclusion that this amount varies much in different individuals; whereas the excretion of exogenous uric acid (from the nucleins of the food) is the same for different individuals. The absolute amount of uric acid excreted therefore depends mainly on the food eaten (Rosenfeld and Orgler, 1896, Sivèn, 1900). In starvation 480 mgms. of uric acid are passed; whilst 600 grms. of meat give rise to 809 mgms., and 1650 grms. of meat to 1230 mgms. of uric acid in the urine. Beef-tea has the same effect as meat, 340 grms. of beef-tea giving rise to 790 mgms. of uric acid (Sivèn). The ingestion of glands rich in nuclei, such as thymus or pancreas, may raise the excretion of uric acid to 2000, 3000, or more milligrams.

The uric acid formed in the body is not necessarily all excreted; it is in part decomposed, burnt up by oxidation, and forms urea. The amount so transformed varies at different times and in different individuals. Hence an increase of uric acid excretion may be due to deficient disintegration of uric acid in the body, as well as to an increased intake in the food or to an increased destruction of the nucleins of the tissues. Whether it may also be due to an increased retention and washing out of uric acid is not so easily determined in health, although this probably occurs in gout and in many allied conditions.

The further question whether uric acid is formed synthetically is also unsettled. The body can certainly form nucleo-proteins, and, therefore, also nuclein bases, from a diet free from nuclein, and from such nuclein bases uric acid may subsequently be produced. But whether it can also be formed synthetically from lower products, such as urea or glycocoll, is not clear in the case of man. Uric acid is certainly produced in this way in birds and reptiles ; the major portion of their nitrogenous excretion is in the form of uric acid, and is of synthetic origin, just as urea is in mammals, this synthesis being effected by the liver. It has been maintained (Wiener, 1899) that the same process also occurs in mammals, and that the difference between them and birds is quantitative not qualitative ; but as yet there is no direct experimental proof that uric acid is so formed. The possible origin of uric acid by synthesis as an alternative to the formation of urea is of special interest in connexion with liver disturbances. It forms the basis of the opinion commonly held, more particularly as the outcome of Murchison's writings, that lithaemia and lithuria are in a special degree a manifestation of liver disturbance — evidence of some altered metabolism (uric acid diathesis). In support of this it may be urged that in certain persons the excretion of uric acid on a purine diet far exceeds the limits observed in health (Lehmann, 1899, and Dapper, 1894), and that this continues for many days afterwards (Rosenfeld and Orgler, 1896). Whether this arises from an increased formation of endogenous uric acid (from the tissues), or from interference with the normal combustion of the uric acid already formed, or from modification of the normal process of urea synthesis and its substitution by uric acid, cannot be definitely decided. As regards the site of formation and disintegration of uric acid, in birds the liver is the exclusive seat of formation of uric acid (Minkowski, 1886). But in mammals the formation of uric acid from nuclein bases is not confined to the liver ; it may take place in most organs, especially, however, in the chief glands (liver and spleen) and in muscle. The formation of uric acid by oxidation is easily demonstrated during autolysis of the liver. The organs which form uric acid are also capable of destroying it, especially the liver, kidney, and muscle. The excretion is affected by the administration of large quantities of butter and sugar in subjects of the uric acid diathesis. It is not affected in any special manner by flushing the system with water. Thus, for the large group of cases included by Murchison under the title of lithaemia, and regarded by him as in a special degree the result of functional disorder of the liver, the functional disturbances which undoubtedly do occur are not necessarily the primary, and may not be even the most important ; in all probability they are really secondary to disturbances initiated elsewhere, perhaps in the gastro-intestinal area. The increase of uric acid and urates may be an evidence of changes in lymph-forming structures, rather than in the liver.

Thus, with regard to the assumed connexion between increase of uric acid and of urates in the urine and liver disturbance, some modification

of our views is rendered necessary in the light of recent knowledge. For some observations indicate that uric acid may have more than one origin in the body—not merely by synthesis of urea and glycocoll in the liver (or kidney, Luff), but independently of the liver from the nuclein constituent of cells generally, especially lymphatic cells. Hence in most cases increase of urates and uric acid represents a disorder of the blood or lymphatic tissues, especially of the gastro-intestinal mucosa, rather than of the liver itself. There is found to be a parallelism between the excretion of uric acid and the number of leucocytes in the blood ; increase of leucocytes after food is accompanied by an increased excretion of uric acid ; diminution of the leucocytes during inanition by a diminished excretion. Quinine, which reduces the number of leucocytes, diminishes the excretion of uric acid ; pilocarpine, which causes a decided increase of leucocytes, increases the uric acid. This connexion between leucocytosis and uric acid excretion is, however, best shewn in leucocythaemia. The excretion of uric acid in this disease is notably increased, sometimes more than doubled ; the source of the uric acid in these cases has been shewn to be nuclein—the substance which forms the main constituent of the nuclear part of cell. The administration of nucleins and foods rich in purine bodies, such as thymus gland, causes an increased excretion of uric acid. According to Horbaczewski, the chief seat of origin is the lymphatic elements of the spleen ; though it likewise appears that all organs of the body contain substances, of the nature of nucleins, capable under given conditions of being split up into uric acid, but none so richly as the spleen. It is probable that the increase of uric acid which rapidly occurs after digestion of food is directly related to the leucocytosis and to increased activity of the lymphatic elements generally (both of the spleen and the gastro-intestinal mucosa) which always occur at this period. The rise in the uric acid excretion is related to this increase of leucocytes, not merely to the food taken ; for in those exceptional cases in which no leucocytosis occurs after digestion of food, the increase in uric acid is also wanting. The increase of urates and uric acid in the urine may thus denote functional disturbance of lymphatic structures rather than disturbance of liver function.

The Excretion of Oxalic Acid.—Importance has long been attached to oxalic acid as a possible evidence of functional disturbance of the liver. Certain clinical symptoms, such as neurasthenia and derangements of digestion, being referred to, or associated with, its presence in the urine. The oxalic acid of the urine is partly exogenous or derived from the food, such as coffee, tea, green vegetables, and partly endogenous or formed by the body itself. The amount of oxalic acid absorbed from the food depends largely on gastric conditions, the larger the quantity of acid formed in the stomach or introduced into it the more oxalic acid appears in the urine ; and its amount is reduced by taking alkalis. But oxalic acid is also found in the tissues, for it is excreted when the food is, practically speaking, free from oxalates. The daily excretion in man in health is about 10 milligrams, and often forms a deposit of oxalate of

lime in the urine, but the quantity of oxalic acid present as sediment is far from being a measure of the total amount present. The separation of crystals depends chiefly on the acidity of the urine, the ratio of calcium to magnesium present, and on the presence of alkalis. The amount of oxalic acid present depends largely on the character of the vegetable foods taken, and on the processes in the digestive tract. Its appearance in the urine is therefore largely the result of digestive processes. It is greatest on a diet of flesh alone, especially gelatine. Another possible source is from the nucleins of purines contained in the food, the substance from which uric acid is also derived. The increased excretion of oxalic acid may be caused by the administration of these bodies. Uric acid itself has long been regarded as a probable source of oxalic acid on account of its behaviour towards oxidising agents in test-tube experiments. That oxalic acid can be formed in the organs has been shewn by the digestive experiments of Salkowski. On adding uric acid to surviving liver, oxalic acid is produced; it can also be produced by digesting uric acid with blood. It would appear, therefore, as if its formation in the body was a secondary reaction due to local disturbance from oxidation processes, possibly in the liver. Another possible source of precursors of oxalic acid are the carbohydrates, specially glucose, and the closely allied compound glycocholic acid. By the excessive administration of these substances by the mouth, the amount of oxalic acid in the urine and especially in the liver (Mayer) is increased. The isolated liver on digestion of glycocholic acid forms oxalic acid. There is evidence, therefore, that both carbohydrates and proteins are possible sources of oxalic acid; that the liver is a possible seat of its formation, and to that extent increase of oxalic acid may be an indication of functional disturbance of the liver. But whilst this is so, it is still doubtful, as shewn by Minkowski (1904), how much of this oxalic acid formation is to be referred to simple fermentative changes in the digestive tract—that is to say, alimentary origin, and how much to true tissue metabolism, *e.g.* of the liver, that is, endogenous. In relation to hepatic disturbance the points of greatest interest are, (1) that uric acid can by oxidation be resolved into urea and oxalic acid; and (2) that this change can be carried out by the liver outside the body in the process of self-digestion (Salkowski).

B. Disturbances connected with Antitoxic and Excretory Functions.—The toxic products formed in digestion or arising from intestinal putrefaction include not merely the recognisable products, such as proteoses and peptones, leucine, tyrosine, glycocoll, xanthine bases, indole, and ammonia, but many others of undetermined nature, the existence of which can only be judged by their effects. The antitoxic function discharged by the liver in relation to such products is of the highest importance. Vegetable alkaloids and putrefactive poisons lose, without exception, one-half or more of their poisonous properties in passing through the liver. The liver converts them into less poisonous compounds, largely by the agency of its carbohydrates. The less glycogen the liver contains, the less its antitoxic power. It regains this

power when its glycogen is increased by administration of sugar. The antitoxic power does not depend on the glycogenic content alone, but also on the whole of protein material of the liver. The toxicity of the urine in cases of severe hepatic disease is increased, poisons, formed during digestion and intestinal putrefaction and usually rendered harmless by the liver, being excreted in the urine.

This power of arresting poisons is one of the most important functions discharged by the liver, as it prevents the escape into the general blood current of crude products of digestion, many of which possess poisonous properties. Thus, Roger (1893), experimenting on guinea-pigs, found that a watery extract of liver was some sixteen times more poisonous than that of muscle, and about five times more poisonous than that of kidney.

There are two sets of observations with regard to the action of the liver upon strychnine: Jaques found that a dose of 0·74 milligram per kilo injected into the portal vein of a dog caused scarcely any noticeable effect, whereas less than the half of this dose (0·36), injected directly into a peripheral vein, killed the animal in three minutes. Roger made a number of comparative experiments on healthy frogs, and on frogs deprived of the liver. (The latter animals live four to five days.) Whereas a healthy frog survived the injection of 0·03 milligram of strychnine for forty hours, a smaller dose (0·02) killed the liverless frog in seventeen hours. The results were still more striking if smaller doses were injected more gradually (over an hour). Thus, a healthy frog received 0·016 milligram subcutaneously without any ill effect; whereas a smaller dose (0·012) killed the liverless one with violent convulsions. As regards atropine, some interesting experiments of Kotliar (1893) made on dogs seem to point to a similar conclusion, namely, that the liver has a protecting power against its action. If the poison were made to pass through the liver, the animal was more resistant than in the case of direct injection into the general blood current. As suggested by Sir Lauder Brunton, some interference with this function of the liver in regard to toxic products reaching it from the intestine is probably accountable for certain of the more common symptoms usually ascribed to disorder of the liver, such as a bitter taste in the mouth, giddiness, cloudiness of intellect, drowsiness, irritability, depression. Products which the healthy liver ordinarily destroys may escape into the general blood.

The importance of the antitoxic functions thus discharged by the liver may be best appreciated when regard is had to the number and variety of toxic products formed within the gastro-intestinal tract in health and disease. The sources of the poisonous substances arising in the gastro-intestinal tract are numerous; they may be obtained from the food-stuffs, or from the secretions and excretions of the body that enter the alimentary canal; and they may be formed either by the digestive ferments or by the bacteria of the intestinal contents. The part played by the liver may be illustrated by the case of ammonia.

As shewn by Nencki and Pawlow, ammonia is formed in all organs, or, at any rate, is present in all. It is small in amount in arterial blood, but is produced in relatively large quantities in the digestive canal. Thence it is carried to the liver, a larger amount of it being found in the portal vein than in any other part of the vascular system. During digestion the quantity of ammonia in the mucous membrane of the stomach and intestine, in the portal vein, and in the liver rises, whilst in most other organs, especially in arterial blood, it remains much the same. The liver, therefore, arrests ammonia, renders it innocuous by converting it into urea, and keeps the ammonia in the arterial blood at a low and constant value. If diverted from the liver by means of an Eck's fistula, the portal blood reaches the general circulation containing a larger quantity of ammonium carbamate. So long as the natural decomposition of albumin, with consequent formation of ammonia, is kept low by a deficiency of protein in the food, marked disturbances in the general condition of the animal do not occur. If, however, flesh be given to the animal, the amount of ammonia present in the arterial blood rises to the height usually found in the portal blood, and then there arises the picture of poisoning by carbamates, namely, coma, catalepsy, amaurosis, and death (*vide also Vol. I. p. 551*). The liver also transforms indole, which has poisonous properties (Herter), into indoxyl-potassium-sulphate or indican, which is excreted in the urine (*vide Vol. I. p. 547*).

Whilst few of the recognisable products of digestion are toxic in any high degree, there is abundant clinical evidence that products of intestinal putrefaction do cause serious functional disturbances in health. The malaise, headaches, giddiness, pains at the back of the eyeballs, the specks before the eyes, the lassitude, the irritability, the disinclination and even inability for work, the feelings of dulness and heaviness, drowsiness, and depression of spirits and melancholia, which so often mark and accompany gastric and intestinal disorder, especially when associated with increased intestinal putrefaction, as in constipation, are in themselves conclusive proof that products are reaching the general circulation which are either not formed in health, or, if so, are being formed in greater quantity than the liver is able to deal with. We have further evidence of the possible toxicity of such intestinal products in cases of intestinal obstruction, in the vomiting, collapse, muscular relaxation, and subnormal temperature which sometimes mark such cases. Although it is not possible to connect these severe toxic effects with any product that can be isolated, it is certain that these effects are produced in this manner. For it has been repeatedly shewn that extracts of the contents of the alimentary canal are exceedingly toxic. However slight their toxicity may be in the small quantities normally formed, their cumulative effect in producing disturbance of the liver—the organ called on to deal with them—must in time be considerable, and this effect is doubtless responsible for many of the chief forms of what is called hepatic inadequacy. Their effect will become the greater if

from similar or independent causes that organ undergoes structural alteration, such as cirrhosis or fatty change. The antitoxic powers of the healthy liver become in this way materially diminished, and the liver is then liable to be disturbed by toxic influences which would not affect the healthy organ. Even apart from the disturbances in the other important functions of proteolysis, glycogenesis, and biliary excretion, disturbances of the antitoxic function of the liver serve to account for many of the most prominent symptoms of functional liver disorder. By every process known to cell defence : by rapid elimination ; by deposition and fixation ; by combination, rendering the substance inert, e.g. of alkaloids and metallic poisons with bile acids or possibly in some cases with glycogen, of aromatic radicles with sulphuric acid, of inorganic poisons and alkaloids, such as strychnine, brucine, and quinine, with bile acids ; by oxidation as a means of destroying bacterial and other toxins ; by neutralisation ; by dehydration, as in the change of ammonium carbamate into urea—by all these processes the liver discharges antitoxic and protective functions, the importance of which to the whole economy cannot be exaggerated, and disturbance of which carries with it not only many well-defined effects of its own, but involves, as will be presently seen, other even more prominent effects connected with disturbances of the associated biliary and assimilative functions of the liver.

Excretion of Drugs and Poisons.—The excretory functions of the liver are not confined to the more or less specific constituents, namely bile, but extend also to medicinal and other substances which may be present in the blood. Thus, it has been shewn that certain drugs, when given by mouth or injected subcutaneously, are to be found in the bile ; for example, ferrocyanide and iodide of potassium, cane and grape sugar, sulphate of copper, oil of turpentine, bromide of potassium, iron, lead, zinc, nickel, arsenic, silver, bismuth, antimony, carbolic acid, salicylate of sodium, toluylenediamine, chlorate of potassium. In some cases this excretion takes place very quickly. Thus, Peiper found salicylate of sodium in the course of half an hour after its administration by the bowel ; iodide of potassium after some six to eight hours. I was able to detect toluylenediamine in the bile within half an hour of its intravenous injection ; and in three to four hours it was present in quite an appreciable quantity. The excretion of metabolic poisons also takes place through the bile, as is shewn by a fall in the toxicity of the bile after ligature of the portal vein.

Another fertile source of disturbance is the excretion of such products into the bile. In relation to the pathology of jaundice and disorder of the bile passages generally, this excretory function of the liver is, I consider, all-important. The power possessed by certain drugs and organic poisons of causing jaundice is, according to my observations, connected with their irritant action on the lining of the bile passages in the course of their excretion by way of the bile. Such poisons usually cause more or less marked changes in the blood. But, as I have shewn, their power of inducing jaundice is proportioned, not to the action on

the blood (phosphorus, for instance, has no haemolytic action at all), not to the amount of haemoglobin set free, not to the amount of bile pigments formed, but solely to the degree of viscosity of the bile induced. It is in this relation that the observations on the excretion of toluylenediamine through the bile are of most interest. This drug is the most notable of all icterogenetic poisons; and my observations with regard to it (1895) shew that the increase of viscosity of the bile, which is the immediate cause of the obstructive jaundice, is the direct result of the irritant action of products in the bile. So irritant, indeed, is its action that, with large doses, an intense inflammation of the duodenum can be set up, definitely beginning at the orifice of the bile-duct where the poison (injected subcutaneously) reaches the duodenum. When the action of the drug is at its height the whole of the intrahepatic ducts are found filled with thick viscid bile. Lower down colourless mucus fills the common duct, and may be seen exuding slowly through the opening of the bile papilla into the duodenum. The duodenum is also filled with similar viscid mucus free from bile; its mucous membrane is acutely inflamed, red, studded with punctiform haemorrhages, and swollen to three times its normal thickness. The whole of the bile passages, in short, are in a condition of acute catarrh, set up presumably by products contained in the bile. For be it noted the catarrh is of intrahepatic, not of duodenal origin. It extends from the smaller ducts down to the duodenum. Affection of the duodenum is indeed by no means necessary. The catarrh and the accompanying jaundice can be produced even when the common bile-duct has been ligatured and a biliary fistula established.

The production of catarrh in this way, by excretion of products in the bile, I consider to be, as I have already pointed out, a most important point in relation not merely to severe forms of jaundice produced by poisons, but to the pathology of liver disorders generally.

The normal products of digestion, carried to the liver and excreted in the bile, are non-irritant. If at any time, as the result of impaired digestion, or still more commonly excessive meat diet, abnormal products are formed in the intestine and absorbed into the blood, the liver has to arrest them, either by modifying them or by excreting them. This function it discharges successfully, and in the great majority of cases probably with little or no disturbance to itself; for it is with crude products that it is accustomed to deal. Did it pour its secretion directly into the intestine, no disturbance would arise,—no further opportunity would be given for any of the abnormal products to produce ill effects. As it happens, however, the bile, with any injurious products it may contain, has to pass at a low pressure along the system of bile passages lined with epithelium, the larger of them having a mucous lining supplied with mucous glands. If, then, such products are formed in increased quantity, as must be the case on an excessive meat diet, and are insufficiently metabolised by the liver, they pass either into the blood or into the bile, and if they have any irritant qualities what-

ever, the effect is to increase the amount of mucus thrown off from the epithelium of the bile passages ; and in proportion to the increase of mucus there is a tendency for the flow of bile to be retarded.

Fortunately certain organic poisons only, and these not common ones, possess irritant qualities to any notable degree. Their action is similar to that of toluylenediamine, in that they cause such an increase of viscid mucus that the flow of bile is temporarily arrested, and jaundice results. The obstruction then is chiefly intrahepatic, and of this nature are, I consider, the various more or less specific forms of jaundice—"epidemic" (catarrhal), probably also ordinary "catarrhal" jaundice ; "malignant jaundice," "febrile jaundice," "infectious jaundice" (Weil's disease), "acute yellow atrophy of liver," also the jaundice of yellow fever, relapsing fever, malaria, pyaemia, and other febrile conditions.

But probably many products of abnormal digestion possess some irritant quality ; falling far short indeed of that above described, but yet capable of producing a certain amount of disturbance. The excretion of these may occasion a certain retardation in the flow of bile, and thus lead to some absorption of bile constituents. This is, I believe, the condition underlying the ailments variously known as "biliaryness," "torpor of the liver," and causing the icteric tinge of the conjunctivae characteristic of these ailments.

It is easy to understand how the liver-cell, which originally had escaped injury, may suffer in its functions secondarily to this condition of the bile and bile passages ; how, in short, many of the classical symptoms of "lithaemia" may arise—not merely a sluggish flow of bile, but also an altered metabolism, evidenced by increase of urates and uric acid in the urine characteristic of the condition ; and how by the continuance of the disturbing factors—faulty products conveyed to the liver on the one hand, retarded excretion along the bile passages on the other—biliaryness may be established as a more or less chronic habit of body. The primary fault lies not with the liver, but with the organ responsible for the products conveyed to it in the portal blood. In these circumstances, to speak of "lithaemia" as a substantive condition due primarily to disorder of liver function, as Murchison did, is hardly justified. The only fault in the liver may be that it merely excretes certain of the abnormal products into the bile, and fails to destroy or modify them on the way. But to excrete can be hardly deemed a primary error of function on the part of an excreting gland.

While, therefore, fully recognising the important part played by disturbance of liver function in disease, it is in my view no less important to recognise the precise relation in which such functional disturbance stands to disease elsewhere. In most cases it is not the primary disorder, but is itself the result of functional disturbance elsewhere ; either in the organs responsible for the products supplied to it, or, as in the cases just considered, in the bile passages.

So far I have considered this condition of intrahepatic (toxaemic) catarrh

solely in relation to jaundice and biliaryness, and to the condition termed lithaemia. I have now to point out that in relation to cholelithiasis and the formation of gall-stones it may also play an important part. In many cases the nucleus around which the deposit of cholesterin takes place is formed of the insoluble body bilirubin-calcium, and in a number of cases the calculi may consist entirely of this material and, unlike the ordinary calculi consisting of cholesterin, which are formed exclusively in the gall-bladder, small masses of bilirubin-calcium are not infrequently found in the intrahepatic ducts, either as "bile sand" or as definite calculi. Moreover, what determines the precipitation of bilirubin in this insoluble form is the presence of albuminous matter. It is thus extremely probable that long-standing conditions of intrahepatic catarrh, by leading to shedding of epithelium, may be the chief etiological factor in the formation of this bile sand. And thus indirectly it may be a potent factor in the production of larger gall-stones; inasmuch as there is reason to believe that, apart altogether from microbic infection of the bile passages, these small calculi of bilirubin-calcium may, in certain cases, by the mechanical irritation they set up within the gall-bladder, lead to the formation of cholesterin.

Conclusion.—Disturbances of the excretory and antitoxic functions of the liver play the chief part in the production of functional disorders of the liver.

C. Disturbances connected with Glycogenesis.—The functions of the liver in relation to the storage and distribution of the carbohydrates of the food are only second in importance to those discharged by it in relation to protein metabolism. The functional disturbances connected with glycogenesis manifest themselves:—(1) *Directly* by disorders connected with carbohydrate metabolism, due to absolute or relative inefficiency of the liver in dealing with the carbohydrate material supplied to it in the food, or conveyed to it by the tissues. (2) *Indirectly* by effects which such disturbances have on the metabolism of fats and of proteins. The most obvious effect of the first class of disturbance is glycosuria. The effects of the latter shew themselves by disturbances of nutrition (loss of weight, or obesity) or by disturbances of proteolytic and antitoxic functions and of fat metabolism.

(i.) *Direct Effects of Disturbance of Carbohydrate Metabolism.*—The carbohydrate of the food is absorbed chiefly as grape sugar, and may undergo combustion, as a large quantity always does, to supply the immediate needs of the body as regards the production of heat and energy. The excess of sugar beyond these immediate requirements is stored up as reserve material in the form of glycogen chiefly in the liver and muscle. By suitable feeding the amount of glycogen in the liver can be increased 10 to 15 per cent or even more. This reserve glycogen is subsequently reconverted into glucose, so that the amount of sugar in the blood is maintained fairly constant at the proportion of about 1 in 1000. When the amount exceeds 3 per 1000 the excess escapes in the urine. In health the power of the liver to deal with the sugar derived from starchy

foods is unlimited. In the case of sugars this is not the case ; there is a "limit of assimilation" varying in the case of different sugars ; and this limit can be used clinically as a test of its functional capacity. In health the liver can dispose of 150 to 200 grams of glucose administered at one time, so that glycosuria does not occur ; but if this limit be passed, sugar appears in the urine. Glycosuria, after the administration of smaller quantities, such as 100 grams, is evidence of some functional glycogenetic incapacity. The defect in such cases may be primarily or for the most part in the liver itself. This is only the case in alimentary glycosuria. In such cases it is usually found that the assimilation of laevulose is more affected than that of glucose ; hence laevulose is more useful in determining "hepatic inefficiency" than is glucose. The limit of assimilation for it is lower (140 to 160 grams) than is that for glucose (150 to 200 grams). The study of glycogenesis has, however, revealed that in health it is not such an independent function of the liver as is, for example, that of urea formation. On the contrary it stands in the closest relation with, and is much affected by, processes in other organs, especially the nervous system, the pancreas, the adrenals, and the kidneys. Hence the disturbances in disease need not necessarily be primarily a disturbance of liver function.

Disturbances of glycogenetic function are met with under the following conditions. In starvation, as has been shewn experimentally for animals (Hofmeister), and clinically in man (Hoppe-Seyler, 1900), the assimilation limit is absolutely lowered. When on a poor diet, some dogs become diabetic, excreting some 30 per cent of the starch of their food as sugar. Temporary glycosuria has also been found in tramps, disappearing in twenty-four hours after their physical condition has become improved. In such cases glycosuria must depend on disturbance of the powers of forming glycogen and of retaining it. The liver is unable to warehouse even the sugar formed in the body from its proteins, and possibly also from its fats. In obesity the glycogenetic power, though absolutely high, may become relatively lowered. The liver is unable to deal with all the carbohydrate material supplied to it, although it is quite capable of dealing with moderate quantities, as well as with that formed from the proteins of the food and the tissues of the body. When long continued, this relative inefficiency may become permanent, and in time an absolute inefficiency. The liver becomes unable to retain any carbohydrates supplied by the food ; there is no glycosuria on a diet free from carbohydrates. This is the condition exemplified by the diabetes of obesity. The influence of the nervous system on the glycogenetic power of the liver is great, as is best shewn by the effect of puncture of the floor of the fourth ventricle in causing glycosuria, and disappearance of glycogen from the liver. If the liver be made to contain little or no glycogen, as may be brought about by starvation, cooling of the body, strychnine poisoning, and febrile disease, no glycosuria follows the puncture. The glycosuria due to puncture is temporary. In disease a large number of nervous lesions are capable of producing glycosuria of a similar temporary

character, lasting from a few hours to five or six days, for example, cerebral tumours, especially of the base, injury to the skull, apoplexies, cerebrospinal meningitis, multiple sclerosis, peripheral neuritis, diseases of the sympathetic ganglia, and last and most important of all psychical disturbances, in Graves' disease, mania, melancholia, hysteria. Toxic conditions, non-infective and infective, play a great part in producing disturbances of glycogenesis. Glycosuria can be induced by giving large quantities of starch to alcoholic subjects, or to patients with influenza or pneumonia.

In liver diseases the function of glycogenesis is affected. Glycogen disappears from the liver in obstruction to the outflow of bile (biliary stasis), and after ligature of the bile-duct from those portions of the liver corresponding to the ligatured bile-ducts. It does not follow that the liver does not still form glycogen, but only that it has lost its power of storing glycogen. It might be expected then that glycosuria would be a frequent accompaniment of biliary obstruction. As a matter of experience this is not the case, nor is it easy in such cases to produce even an alimentary glycosuria by administration of large quantities (150 grams) of cane sugar (von Noorden, 1893; Strauss, 1901). On the other hand, patients with liver disease have a lower limit of assimilation for laevulose than healthy individuals; 80 per cent of these patients react towards addition of laevulose by excretion of sugar, whilst in 4·5 per cent only of all hepatic cases is it possible to produce an alimentary glycosuria with glucose. The glycogenetic power in liver disease is, however, on the whole remarkably stable and constant, even in diseases, such as cirrhosis, involving destruction of liver substance. On an ordinary diet a patient with cirrhosis does not excrete sugar unless there is coincident diabetes, as in "bronzed" diabetes of haemochromatosis, due to chronic pancreatitis. On the other hand, alimentary glycosuria after small doses of glucose has been noted by many observers to occur more readily in cirrhosis than in healthy subjects. This may be due to the establishment of the collateral circulation allowing the passage of sugar directly into the general circulation. The results of observers are, however, discordant; those of more recent observers who have not been content with ordinary reduction tests, but have employed more reliable tests, have been negative. It is therefore still doubtful whether alimentary glycosuria is somewhat frequent, or, as is more probable, rare in cirrhosis. It is certain at any rate that in some cases of advanced cirrhosis it is not more easily obtainable than in healthy subjects.

In other conditions of liver disease involving destruction of its substance, such as carcinoma, or interference with its functions, such as fatty liver, Lépine found it impossible to produce alimentary glycosuria.

(ii.) *Indirect Effects of Disturbance of Glycogenesis.*—On fat metabolism and proteolysis.—When carbohydrate metabolism is disturbed, the synthesis of fat is also thrown out of gear. For fat is formed from the carbohydrate not at once used up or converted into glycogen. Hence,

next to fat, the most powerful fat-producer is carbohydrate—a conclusion now definitely ascertained and applied extensively in therapeutics. The change is a gradual one, and in most cases occurs only when carbohydrates greatly exceed the needs of the tissues. There is no conclusive evidence that in health this change occurs unless carbohydrates are not in excess. In disease, however, for example diabetes, it is possible that sugar may be burnt off by becoming first converted into fat (Naunyn, 1899; von Noorden, 1901) by a conjoint process of reduction and synthesis akin to that which occurs in butyric-acid fermentation. This change most probably takes place in the liver, since similar processes have been proved to occur there after death.

Disturbances of glycogenesis—whether arising from defective storage or increased glycolytic changes—are therefore always attended by disturbances in fat metabolism, in the first instance by diminished formation of fat, and later on by increased call upon the fat already present in the body to take the place—for purposes of combustion and nutrition—of the carbohydrate lost to the body. More or less wasting is thus a characteristic effect of all disturbances of glycogenesis. In the case of fats, the deficiency or loss of carbohydrates leads to the transference by the blood of the fat deposited in the tissues to all the organs requiring it, but especially into the liver. This transference of fat may induce the lipaemia met with in some cases of diabetes, and possibly be a mechanical cause of severe symptoms by means of fat-embolism. Further, and this is more important, there is excessive metabolism of fats for purposes of combustion, and with this a corresponding excess of the products of fat metabolism, among which are the so-called acetone bodies, diacetic acid, acetone, β -oxybutyric acid. The greater part of these bodies have fatty acids as their immediate precursors, and the liver is the site of their formation from fat (and from protein derivatives). The essential factor in causing acetonuria is the absence of proper carbohydrate metabolism. The effects on liver function of the acidosis thus produced are various. Some of them have already been seen in connexion with its metabolism of urea and ammonia (see p. 33). The most dangerous result is diabetic coma. The body is able to protect itself up to a certain point against this increased production of acids, by neutralising them with ammonia. This combines with the acids and is excreted in the urine to the amount even of 10 to 12 grams daily, instead of the average 0·5 gram (*vide "Acidosis," Vol. I. p. 543*). Notwithstanding the protective power of the ammonia, the alkalinity of the blood may become absolutely diminished, and then there follow the phenomena of acid intoxication presented in diabetic coma. Short of these extreme effects, the diminished alkalinity of the blood caused by increased formation of acids may in certain cases, as has already been seen (p. 23), involve grave disturbances of the proteolytic functions of the liver, to the extent even of becoming the main factor in determining the occurrence of the gravest of all liver disturbances, viz. that of acute yellow atrophy.

Both directly and indirectly defective glycogenesis may thus be

responsible for some of the gravest disturbances—both functional and structural—to which the liver is subject.

(i.) Absence or deficiency of carbohydrate material (glycogen) in the liver-cell involves an increased destruction of protein material, with consequent wasting of the body. (ii.) This increased proteolysis involves an increased formation of toxic products, with consequent increased liability to toxic effects producible by such products. (iii.) The absence of glycogen from the liver-cell, by diminishing the combustion processes, interferes with the destruction of toxic products, and this involves a diminution in the antitoxic powers of the liver-cell. The starving animal is more easily affected by poisons than the well-fed (glycogen-rich) animal. (iv.) From the loss of carbohydrate material caused by impaired glycogenesis (and the glycosuria of disease) extensive changes in fat metabolism result. The increased metabolism of fats thereby necessitated gives rise to an increased formation of acids, and if long continued the acidosis thus occasioned may produce symptoms of acid intoxication of milder or severer degree. It may even, in favourable circumstances, be the chief factor determining the onset of the severe structural changes characterising acute yellow atrophy, delayed chloroform poisoning, and other severe liver conditions.

D. Disturbances connected with the Metabolism of Fats.—These play a far more important part in producing grave functional disorders of the liver than was formerly supposed.

The Physiology of Fat Metabolism.—The neutral fats absorbed with the chyle remain in the blood for a brief period, till they are selected for combustion or storage in the subcutaneous tissues, para-peritoneal spaces, and the liver. During fasting, the fat streams from the depots back into the blood, to all the organs requiring it. A condition of lipaemia is therefore constant, and becomes very manifest in fasting, in phosphorus and phloridzin poisoning, in alcoholic intoxication, and in diabetic coma—conditions in which there is more or less widespread inanition, especially with deficiency of carbohydrates. Certain fermenters have been found in the blood capable of splitting the fat and rendering it soluble. And fermenters of this nature have been found in the liver. In these conditions, as has been shewn by Rosenfeld (1895-97), an extensive passage of fat takes place from the fat deposits of the skin and abdomen into the liver, and the latter becomes loaded with enormous quantities of fat (to the extent of 70 per cent of its bulk). The distinctions formerly made between fatty infiltration and fatty degeneration no longer hold good (*vide Vol. I. p. 575*). This excessive storage of fat in the liver occurs only when the glycogen has disappeared from the liver, and it can be prevented if the animal be fed with substances, such as sugar, from which glycogen can be readily formed. This storage of glycogen and fat would thus appear to stand in a certain antithesis. Although in certain cases large quantities of fat may often be found along with extensive storage of glycogen, for example, in the livers of Strassburg geese (Magnus-Levy), yet generally excess of fat in the liver denotes

deficient glycogenesis. The storage of fat in the liver may be explained in two ways : (a) that the liver must first transform the fat molecule in some way before it can be consumed by the cells (Nasse), possibly into carbohydrates ; (b) that the storage of fat in the liver is a reserve readily available to meet any sudden call upon the metabolism, as for example that entailed in violent exercise ; it has been suggested that the fat can pass much more quickly and easily from the centrally situated internal and vascular liver than from the cells of ordinary adipose tissue.

Transformation of Fat into Sugar.—The question whether this occurs has been much disputed. The organism in diabetes eliminates more sugar than it has taken in from the food or can possibly have from protein or other sources. Although this is not proved, the possibility of the formation of sugar from fat must be admitted. The body possesses such an urgent need for carbohydrates that it attempts to meet this in all possible circumstances ; if it cannot get it from sugar, it takes it from protein ; if both fail it may even take it from fats. An increase in the amount of fat-containing food does not produce either an increased formation of sugar or an accumulation of sugar.

The Pathology of Fat Metabolism.—The disturbances that arise in connexion with fat metabolism in the liver are evidenced chiefly by the excretion of acetone bodies, namely, acetone, aceto-acetic acid, and β -oxybutyric acid, and by the condition of acidosis to which their formation in excess gives rise. Of these bodies only acetone can be found in the urine in health (about 1-3 centigrams daily). The conditions under which these bodies are increased are essentially those in which the oxidising powers of the body are reduced by some notable deficiency or absence of carbohydrates from the food. Deprivation of food or the exclusion of carbohydrates from the food causes acetonuria without exception in the case of man, also in children, also during pregnancy and labour, also after injury of the central nervous system, also after the administration of narcotics. In all these cases the administration of carbohydrates, starch, and especially sugar, removes within a few days this form of acetonuria. If it be allowed to continue, there also occurs an excretion of aceto-acetic acid and oxybutyric acid. These acids are derived from the fat of the body. In general it must be distinctly emphasised that an increase of the fat in food has no material influence on the formation and elimination of the acetone bodies. This depends in the first place upon the internal condition of the cell, and this condition is affected by a deficiency of carbohydrates, and therefore in the liver by deficiency of glycogen. The extent to which the metabolism of fats is affected in diabetes and diabetic coma may be judged from the observation that no less than 342 grams have been found in the urine in the course of three days (Magnus-Levy). The fats therefore yield the chief material necessary for the formation of acetone bodies, and their formation in any notable quantity is in the first place caused by lack of carbohydrates. They are not formed in the intestine.

They may possibly be formed in all organs, but the chief seat of the formation is the liver and muscles.

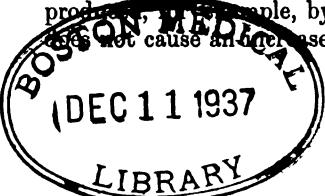
Disturbances in hepatic fat-metabolism are thus primarily connected with deficiency of glycogen whether arising from want of carbohydrates, as in starvation, or from excessive loss of sugar, as in diabetes. The conditions in which increased acidosis arises are conditions especially affecting glycogenesis, such as poisoning with carbonic oxide, extirpation of the pancreas, poisoning with phloridzin, exclusive feeding on animal fats, and lastly, severe cases of diabetes. The symptoms produced in severest cases are those of diabetic coma. In these conditions, owing to the absolute deficiency of carbohydrate and the excessive transference of fat from the tissues to the liver, the acidosis is absolutely excessive. The proteolytic functions of the liver, however, are fully maintained.

The chief interest of such disturbances of fat metabolism as an evidence of functional disturbance of the liver arises when an acidosis of lesser degree is combined with disturbance of proteolytic activity of the liver-cell. This is the condition presented in the final stages of severe hepatic disease such as cirrhosis, acute yellow atrophy, phosphorus and chloroform poisoning. A disturbance in fat metabolism (with increased acidosis) which would not affect a fairly healthy liver-cell becomes then much more important. At a time when the intracellular alkalinity of the liver-cell is already at a low level, as the result of inanition, deprivation of food, and diminished absorption of ammonia in the portal blood consequent thereon, the additional acidosis arising from excessive fat metabolism may—as already described—suffice to lower the alkalinity below the point necessary to keep its own proteolytic ferments in check. There then results self-digestion or autolysis of the liver-cell by its own ferments; with complete arrest of all its functions. The clinical picture then presented, in slighter or severe degree, is not that of acidosis as a diabetic coma, but that of acute yellow atrophy and chloroform poisoning, namely, essentially one due to the abolition of all the antitoxic functions of the liver.

This conclusion as to the relation of disturbances in fat metabolism to the severest forms of liver disturbance represented by acute yellow atrophy and chloroform poisoning is of great practical importance. The vomiting which occurs after administration of anaesthetics is not of nervous origin, but is, I consider, essentially toxæmic; due to the profound depression of liver function with consequent diminution in its antitoxic function during the period of the administration.

E. Disturbances Connected with Biliary Function.—The physiology of the bile is referred to elsewhere (Vol. III. p. 287), but it is advisable to sum up the influences causing an increase in the quantity of bile; the three chief are increased supply of water, the absorption of bile or bile salts, and the absorption of the food products.

The action of water is not a direct one; mere wateriness of blood—produced, for example, by injection of water directly into the blood—does not cause an increased flow of bile. So that its effect in increasing



the flow when administered by the mouth or by the intestine is probably due to products washed out from the intestinal walls and carried to the liver. To get the full effect of this action of water in diluting the bile, care should be taken not to give the water with the food. Food alone causes an increased flow of bile ; for instance, the most copious flow is during the day, and a fall takes place during the night ; nevertheless it is during the night that the bile is richest in solids. If, then, our object be to increase the fluidity of bile, that object is best attained by giving water when the natural tendency is for the bile to become more concentrated, that is, either between meals or at night time several hours after the last meal. As a matter of clinical experience I have found this practice yield the best possible results ; for example, in cases of jaundice due apparently to highly concentrated bile and "biliary sand" in the bile-ducts.

So far as drugs are concerned, some few (salicylate of sodium, benzoate of sodium, turpentine, olive oil) seem to possess the power of exciting an increased flow of bile ; but the action of most other so-called cholagogues is uncertain, and, even in the case of those above mentioned, their mode of action is quite undetermined.

Consideration of the various agents capable of exciting an increased flow of bile is important, for in combating disease it is often necessary to counteract factors which tend to lessen the flow of bile.

(i.) *Diminished Flow of Bile.*—Some interesting information regarding the mechanism underlying bile secretion is obtainable from a study of the factors concerned in reducing the quantity of bile ; and to these I must now draw attention.

Influence of Fever.—All observers are agreed that fever diminishes the secretion of bile. Thus, in a case of a biliary fistula recorded by Eiffelmann it was noticed that on the onset of pneumonia, and again of an attack of dysentery, the flow of bile ceased. In the case recorded by Paton and Balfour the patient suffered from time to time from feverish attacks, and this condition had the most distinct effect upon the amount of bile excreted. During the eleven days of the first attack the amount fell from an average of 650 c.c. to 475 c.c. a day, while the solids fell from 8 and 9 grams to 3·7 grams. The subsequent restoration to the normal was slow. In a second attack, on a rise of temperature to 99·6° F., the bile fell from 592 c.c. to 238 c.c., and the solids from 9·2 to 3·2 grams.

These observations agree with the experimental results obtained by Pisenti (1886), who finds that fever invariably causes a diminution in the excretion of bile—the diminution being one-third to one-half the normal. This diminished excretion of water appears to be the result of fever itself, irrespective of its nature ; the diminution in the amount of solids, on the other hand, appears to depend upon the nature of the fever. Moreover, in fever the bile always contains a larger amount of mucin ; and the colouring matters seem also to undergo alteration, the bile becoming much darker, almost black ; sometimes of a dark-green colour.

All these changes are purely functional, as examination of the liver failed to reveal any organic change.

Influence of Poisons.—A varying and sometimes notable concentration of bile has been shewn by Stadelmann to be one of the chief features of the action of haemolytic poisons generally. Thus, after injection of haemoglobin, for the first ten hours there is no obvious change in the bile; then the quantity falls, and the bile becomes thicker, more concentrated, and very dark in colour: this variation continues for twenty-four hours, the bile being reduced to one-third its normal amount. (At the same time the bile pigments are greatly increased by as much as 56 per cent, the bile acids being diminished by about the same amount.)

Toluylenediamine—a drug possessing marked haemolytic and icterogenous properties—causes notable changes. In the first stage, lasting about twelve hours, the bile is increased in quantity (and is very rich in pigments); then follows a second stage, during which the flow appears to lose all the characters of bile, and is composed of a small quantity of extremely viscid colourless mucus. After sixty to seventy hours the bile gradually regains its normal character.

Phosphorus also is found to act similarly; at first it causes an increase of bile; the bile then falls to one-fifth of its former amount, and becomes clearer and more mucoid.

The action of arsniuretted hydrogen is also attended with a remarkable concentration of bile, the gall-bladder and bile-ducts being filled with thick viscid bile, which frequently contains large quantities of amorphous sediment as well as numerous crystals of bilirubin. The bile is reduced to as much as one-fifth its former amount (while the bile pigments are increased to as much as $3\frac{1}{2}$ times, and the bile acids are diminished to as much as one-tenth of their former amount). The importance of these observations in connexion with the jaundice produced by poisons I shall discuss fully elsewhere (art. "Jaundice").

These observations have, however, an importance in relation to the whole of the class of liver disorders attended with a diminished flow of bile—for no factor is more important in producing functional liver disorders than this of diminished secretion of bile. The troubles it occasions arise not so much from diminution of the output of the specific constituents of the bile—the bile pigments and bile acids—for the former, indeed, are usually much increased while the latter are usually even more markedly diminished, as from the temporary stagnation of bile which gives opportunity for the absorption of its constituents, and reacting on the liver-cell disturbs its functions.

What, then, is the cause of this diminished flow? Is it the result of a specific action of the poison on the hepatic cell, whereby its excretory function is temporarily arrested? That the action is in some degree specific seems to be indicated by the remarkable difference in the behaviour of the chief bile constituents; the bile pigments are usually notably increased, thus indicating great activity of the liver-cell in taking

up and destroying the haemoglobin conveyed to it, while the bile acids on the other hand are no less remarkably diminished, indicating a lessened protein metabolism within the cell.

It is possible that by the direct action of a poison the excretion of water may be temporarily lessened. The concentration of the bile in such cases may then be due in part to a lessened aqueous excretion on the part of the hepatic cell. But the chief cause underlying it I believe to be an increased formation of mucus by the epithelium lining the bile passages. The action of the poison is not limited to the hepatic cell, but extends to the lining of the bile passages. As already shewn (p. 41), the bile is an important channel for the excretion of poisons and drugs present in the blood; and it is the excretion of such more or less irritant products that is apt to excite catarrh of the bile passages, increased formation of mucus, and consequent increased viscosity of bile.

If the excreted products be harmless, their passage along the bile-ducts is without ill effect on the lining epithelium. If, however, they possess any irritant properties they will tend to excite increased secretion of mucus, not only from the mucous glands of the larger bile-ducts and the gall-bladder, but from the epithelium of the smaller bile passages; and in proportion to their irritant character and the resulting increase of mucus will be the tendency for the flow of bile, excreted under very low pressure at all times, to be retarded, and for the bile thus to become more concentrated.

Such, briefly, I consider to be the way in which the amount of bile can be diminished by changes in the bile passages. In ordinary circumstances the only effect is to favour and promote absorption of its water as it passes along them. If it pass a certain degree, however, some of its bile constituents may also be absorbed; and thus arises the slight icterus of the conjunctivae (from absorption of some bile pigment) characteristic of the condition termed biliousness.

If the conditions underlying these changes persist or frequently recur, then the ill effects of diminished wateriness of bile extends beyond the production of mere "biliousness." Repeated irritation of the lining of the bile passages by such products tends to promote a chronic tendency in the bile passages and in the gall-bladder (where the bile rests for some time and becomes more concentrated) to catarrh. The basis is thus laid for the production of some of the chief changes in the bile which underlie the formation of gall-stones; these are stagnation of bile, increased formation of cholesterol by the epithelium of the bile passages, precipitation of bilirubin-calcium, and presence of inspissated mucus.

Summary.—Our consideration of the chief conditions influencing the amount of water in the bile has thus led to some important conclusions.

1. There is no evidence that any disturbance ever arises from too great an excretion of water in the bile, if indeed such dilution ever takes place.

Older writers recognised the existence of a "polycholia"—an increased flow of bile—and were disposed to attribute certain ill effects

to it,—notably an increased absorption of bile pigment from the intestine and the production thereby of a form of jaundice (Frerichs). As I shall shew later (art. "Jaundice," p. 90), the origin of a jaundice in this way is exceedingly doubtful. It is true one important form of jaundice—that connected with blood disorder and increased destruction of haemoglobin—is frequently associated with an increased flow of bile rich in colouring matters. The essential change of the bile in such cases is, however, not increase in its quantity, but increase in its pigments. It is not a polycholia, which is a name only rightly applicable to an increase of all the bile constituents, but a polychromia; and the jaundice so frequently associated with this change is due, not to increased absorption of bile from the intestine, but to absorption from the bile passages as the result of increased viscosity. So far from any aqueous dilution ever being a cause of disturbance, it is the one condition of bile which all our efforts are directed to produce; and the task is by no means easy.

2. On the contrary, one of the most potent factors in hepatic derangement is diminished fluidity with lessened flow of bile. This may be the outcome of defective excretion on the part of the liver-cell; and such is probably its character in fever, in which the amount of bile is always diminished.

But another and, in my opinion, more common and potent factor is increase of resistance to its flow (at all times under very low pressure) along the bile passages. This increased resistance may arise from one of two sources: either from sluggish peristaltic action of the walls of the bile-ducts (and gall-bladder?), one of the most important factors in the passage of bile from the bile-ducts; or from increased formation of mucus, and corresponding abnormal viscosity of bile.

Both these conditions, but more especially the latter, underlie the state of "biliaryness"; and the increase of mucus is the result of the irritant action of products excreted in the bile. For the formation of these products in the first instance the liver may not be in any way responsible: they have been formed elsewhere; they reach it in the portal blood, and it has duly excreted them. But disturbance of the antitoxic function of the liver is probably largely responsible for the excretion of these products. In health they are destroyed in the liver, or form combinations which deprive them of their poisonous qualities. Were it not for their irritant action on the bile passages in the course of their excretion, few or no ill effects might be produced. But the increased formation of mucus excited by their action as they pass along the bile passages has as its result an increased viscosity of bile—a retardation of its flow and a diminution of its quantity.

Whether, then, the diminution of bile be caused directly by impaired action of the liver-cell, or indirectly by increased resistance in the bile passages, it is important to note that the primary cause of the mischief is not necessarily the liver itself. The disorder is set up by products conveyed to it in the portal blood. Thus all agents which promote

healthy action of the gastric and intestinal mucosa may, by preventing the formation and absorption of abnormal and possibly irritant products, and by freeing the liver and its bile passages from their injurious presence, promote an increased flow of bile, and thus indirectly have a cholagogue action.

(ii.) *Disturbances connected with Variations in the Quantity of Bile Pigments.*—(a) Increased Formation.—*Polychromia* and its Relation to Jaundice.—For the information we possess as to the variations that occur in disease, we are indebted mainly to observation of the pigments present in the urine; but we have also a few observations made directly. Thus, a large increase always follows the injection of haemoglobin into the blood, or again, of haemolytic agents that set free haemoglobin, such as distilled water, toluylenediamine, and arseniuretted hydrogen (Stadelmann). This increase may run as high as three to four times the normal amount. It usually makes itself manifest in from 3 to 4 hours after the injection of the haemoglobin. If the injection be merely subcutaneous it is later—12-14 hours. This “polychromia,” as it has been named by Stadelmann, is not necessarily accompanied by an increase of bile; on the contrary, the bile is generally diminished in quantity and highly concentrated—sometimes to a notable degree. Even more remarkable is the behaviour of the bile acids; instead of being increased, they are reduced to mere traces. Great activity of the liver-cell in one direction (formation of bile pigment) is thus compatible with lessened activity in others (excretion of water, formation of bile acids). These observations are of special interest in regard to the bile acids. Absence of bile acids has usually been regarded as an important evidence of inaction of the liver; and hence came the notion that jaundice without bile acids in the urine denotes that the bile pigment must have been formed elsewhere than in the liver (“haematogenous jaundice”). It is now made clear that no such significance attaches to the absence of bile acids; their defect is quite compatible with a greatly increased formation of bile pigments by the liver. A similar increase of bile pigments is a feature common to all conditions in which blood-destruction is increased. According to my observations, it is a constant and most notable feature of the bile in pernicious anaemia; in no morbid state does the bile possess such extraordinary staining power as in this disease. An increase of bile pigments likewise attends the absorption of large extravasations of blood, and is a feature also of most of the forms of jaundice caused by poisons.

It is in relation to jaundice that the chief interest has hitherto attached to this increase of bile pigments. The occurrence of jaundice in association with excess of bile in the stools has long been noticed; it constitutes the “jaundice from polycholia” of old writers. The doctrine taught by Frerichs was that the jaundice in such cases is due to excess of bile pigments, their increased absorption from the intestine, and their deficient disintegration in the blood. The later form of this teaching is that bile pigments are absorbed in such excess that the liver is unable to excrete them all, so that some escape through the liver into the general

circulation and produce the jaundice. These doctrines I shall discuss more fully elsewhere (*vide* art. "Jaundice," p. 72). At present I will only say that, in my opinion, there is no sufficient evidence that jaundice ever arises in this way. Some bile pigment is probably always absorbed from the intestine to be excreted again in the bile; but the extent to which such an absorption occurs is doubtful, and in all probability has been much exaggerated. It may be regarded as certain, however, that any pigment so absorbed is excreted again, for the liver rapidly takes up and excretes any bile pigment present in the blood. Thus, bilirubin injected directly into the blood is entirely excreted through the bile in from two to four hours after its injection. Similarly, the increase of bile pigments following injection of bile into the duodenum, as shewn by Schiff and Rutherford, is always greater when bile is introduced than when a corresponding amount of bile salts are so introduced.

In the absence, then, of any other explanation of the jaundice with polycholia, we might attribute it to an increase of this absorption—of this "circulation of bile pigment." But Stadelmann's observations shew that drugs which cause polychromia usually cause other changes in the bile—one of the most notable being that at one time or other there is a remarkable increase in its viscosity, leading sometimes to arrest of its flow. It is this arrest that causes the jaundice. The jaundice results from absorption of bile from the bile-ducts, not from the intestine. Both preceding and following this stage of increased viscosity there is a greatly increased excretion of bile pigments; hence the abundance of bile pigment in the intestines, so frequently noted in these cases. The "jaundice of polycholia" is thus hepatogenous (obstructive), and is not due to an increased absorption from the intestine.

Excretion of Haemoglobin into the Bile.—I have now to point out, with regard to this action of the liver on haemoglobin, that it is not simply a question of mere amount—of so much free haemoglobin in the blood, with resulting formation of so much bile pigment. Increase of bile pigments is not necessarily proportionate to the amount of free haemoglobin in the blood. Thus, the injection of distilled water or pyrogallic acid produces intense haemoglobinaemia with haemoglobinuria, but only a moderate increase of bile pigments. On the other hand, toluylenediamine, which in dogs causes but a moderate blood-destruction without haemoglobinuria, causes a large increase of bile pigments. Thus it appears that the liver can be specially stimulated, and that the amount of bile pigment formed depends not only on the amount of free haemoglobin available, but also on the activity of the liver-cell. In certain circumstances this latter element may be so affected that haemoglobin passes unchanged through it into the bile. This condition of "haemoglobinchia" is usually the result of the action of certain severe poisons. Thus, according to Filehne (1889), after poisoning with phenylhydrazine, toluylenediamine, aniline derivatives, pyrogallic acid, chlorate of potassium, and glycerin, all agents intensely haemolytic in their action, haemoglobin is constantly found in the bile. The same results, after poisoning with aniline and

toluidine, have been found by Wertheimer and Meyer (1890). I produced such a "haemoglobinchia" in one instance by ligaturing the hepatic artery and then injecting distilled water. All these observations apply to rabbits. In dogs, on the other hand, Filehne could never find any free haemoglobin in the bile.

This passage of haemoglobin unchanged through the liver-cell into the bile must be regarded, then, as betokening a grave disturbance of liver function. It is probably an extremely rare process in disease, and is probably confined to the last stages of such severe toxic conditions as acute yellow atrophy and the severest forms of toxic jaundice. But apart from these extreme effects, this occurrence, rare though it be, is of interest as denoting that the activity of the liver in breaking up haemoglobin can be directly influenced by drugs.

In what way the destruction is effected within the liver-cell we have no definite knowledge. As I have pointed out, an increased formation of bile pigments may occur while the formation of bile acids is diminished, indicating that the two processes, of haemoglobin-destruction and breaking up of protein material, respectively underlying these, are to a certain extent independent of each other. Nevertheless certain interesting observations no less clearly indicate that the activity of the liver-cell in breaking up haemoglobin depends upon its general nutritive activity. Schmidt and his pupils have studied the action of liver-cells on haemoglobin outside the body, and they find that the destruction of haemoglobin (and formation of bile acids) is much increased by the presence of glycogen, and still more of grape sugar; in the absence of these, indeed, the destruction of haemoglobin ceases.

(b) Lessened Formation of Bile Pigments.—Among the conditions which appear to diminish the amount of bile pigments I have again to note fever. This sequence was very noticeable in the case of biliary fistula recorded by Paton and Balfour. Irregular attacks of fever occurred from time to time, and during these the bile not only fell in quantity, as also in the amount of solids, but became obviously pale; on several occasions, indeed, quite colourless.

This diminished formation of bile pigments is of special interest in relation to the conception of jaundice by suppression. This theory took its origin when it was thought that the bile pigments existed preformed in the blood, and that the only function of the liver was to excrete them. If the liver ceased to act, the pigments accumulated in the blood, and jaundice ensued. It is now certain that the bile pigments are formed by the liver, not within the blood. But the conception of a jaundice by suppression is still held by many; and the form it now takes is that any temporary inaction of the liver in forming bile pigments is bound to throw pigments into the circulation which would otherwise have been excreted; whereby jaundice is induced. Now I have shewn one possible effect of such inaction, namely, that haemoglobin passes through the liver-cell unchanged. But such an event is only producible experimentally by the action of severe poisons, and even then with difficulty; in disease it

is probably of the rarest occurrence. The other possible effect is that illustrated by the action of fever, when less bile pigment is formed. There is no evidence, however, that such a diminished formation of necessity produces jaundice. On the contrary, in the case of the great majority of poisons that act most severely on the liver-cells, and are most likely to cause suppression of function, there is direct evidence that they stimulate the liver to an increased formation of bile pigment. The jaundice they give rise to is not a jaundice of suppression, but one of increased activity with increased viscosity of bile consequent on the action of the poison on the intrahepatic bile-ducts (toxaemic catarrh).

(iii.) *Disturbances evidenced by Qualitative Variations in the Bile Pigments.*—The changes in the bile pigments in disease are not restricted to mere variations in quantity. They extend also to the quality of those formed and the quality of the urinary pigments derived from them.

In health, as we have seen, the chief pigments are bilirubin and biliverdin. Within the intestine these are reduced by the action of the micro-organisms present to urobilin (stercobilin)—the colouring matter of the faeces.

Relation of Bile and Urinary Pigments.—Increase of the pigments of the urine (for a description of which see subsequent article on "General Pathology of the Renal Functions") is a common feature of liver disorder. The questions that now present themselves are:—Does the increase of such pigments indicate disorder of hepatic function especially; or, on the other hand, indicate merely disorder of intestinal functions? Or as it may otherwise be put:—To what extent are these pigments derived from the bile pigments within the intestine, and thus only indirectly from the liver? Or, are they the direct products of hepatic metabolism, formed by the liver just as bile pigments are?

With regard to urobilin—the chief representative of these urinary pigments, and the one which has been most fully studied in disease—an increase is found in the urine in a number of conditions, such as fever, absorption of blood, pernicious anaemia, febrile forms of jaundice, and the action of certain drugs, such as trional. These conditions are chiefly such as are marked by some increased destruction of blood. The increase of urobilin may denote merely an increase of bile pigments with an increased formation of urobilin from these within the intestine, and not necessarily any disturbance of hepatic function. A notable increase of bile pigment takes place during absorption of extravasated blood, as shewn by Stadelmann; and according to my observations in pernicious anaemia no feature is more constant or more striking than the extraordinary colouring power of the bile, denoting great richness in pigments.

There are other facts, however, which denote that the intestine is not the only seat of origin of urobilin; it is also formed elsewhere in the body. Thus, in cases of obstructive jaundice in which no bile enters the intestine urobilin is still found in the urine. In the case of biliary fistula described by Copeman and Winston no bile entered the intestine, nor was any bile pigment to be found in the urine. All the bile escaped through

the fistula. Nevertheless the urine remained of normal colour, and its colouring matters must therefore have been formed elsewhere than in the intestine. In these circumstances it is assumed that the pigment has been formed within the liver itself, as a direct product of hepatic activity. And it is from this point of view that so much interest is attached by some observers to increase of urobilin (and other pigments) in the urine in relation to hepatic disorder; for an abnormal increase of urobilin may thus denote not merely an increase of bile pigments, but also an abnormal activity of the liver-cell, and may be an index of hepatic disorder. Thus urobilin has been regarded as essentially the pigment of a diseased liver (Hayem). Its formation by the liver may, I think, be thus conceived. Formed in small amount in health, as a by-product in the course of the formation of bile pigment by the liver-cell, in disease it may be formed in disproportionately large amount, not from the bile pigments, but, so to speak, at the expense of the bile pigments. An increase of urobilin in the urine may denote not merely an increased haemolysis with an increased formation of bile pigment—this it necessarily does—but it may denote, further, some hepatic inefficiency in dealing with the haemoglobin or pigments derived from this haemolysis. I would point out a third alternative:—The conditions in which it is chiefly met with—toxic forms of jaundice, pernicious anaemia, and the like—are chiefly those denoting marked disorder of the blood, and the fault may possibly be not so much increase of bile pigments (intestinal origin) or hepatic inefficiency (hepatic origin) as some abnormal character of the haemoglobin and other pigments set free within the portal area and conveyed to the liver in the portal blood. I consider it to be probable that some part of the urobilin and chromogens of the urine is normally formed within the portal area, notably within the spleen, where, according to my observations, haemolysis is most active; and their increase in disease may denote abnormal blood changes antecedent to any subsequent hepatic inefficiency.

In deciding to which of these various possible causes urobilinuria is due in any particular case, we must be guided, I think, by the general characters of the symptoms rather than by any particular view as to the source of urobilin. Thus, in absorption of extravasated blood I regard the urobilinuria as not necessarily of the same significance as it has in severe forms of febrile (toxaemic) jaundice. In all cases it denotes increased haemolysis. But subject to this, it may in some denote intestinal derangement—increased putrefactive changes, with increased formation of urobilin from the bile pigments within the intestine; in others it may denote abnormal haemolysis with formation of abnormal pigments in the tissues (extravasated blood) or in the spleen; and lastly, in a third group it may possibly denote hepatic inefficiency in dealing with the haemoglobin supplied to it. The data we possess, then, by no means justify the view that urobilin is essentially the pigment of hepatic disorder.

Bilirubin Calculi.—Before passing from this subject of the variations in the character of the bile pigments presented in disease, and their

possible significance in relation to disorder of the liver, I must refer to one other modification of a qualitative character, which may not only denote but actually be the immediate occasion of severe disorder of the liver; I refer to that change which leads to the precipitation of bilirubin in insoluble form within the intrahepatic bile-ducts or within the gall-bladder, and to the formation of bilirubin calculi.

Bilirubin itself is never precipitated; but under certain conditions it forms a combination with calcium, and is then precipitated as an insoluble compound. In this form it is the nucleus of a considerable proportion of the ordinary gall-stones; in a smaller proportion it is itself the calculus, and may constitute the gritty particles—the so-called biliary sand—found within the intrahepatic ducts, or the small calculi found either in these ducts or in the gall-bladder.

Two forms of these calculi are met with; in the one the bilirubin-calcium is mixed with cholesterol, as much as 25 per cent of the latter being present; the remainder being made up of bilirubin-calcium, usually with small quantities of copper and traces of iron. The calculi of this kind are usually of large size, as large as a cherry or larger; and lie singly, or at most in groups of three or four, in the larger bile-ducts or gall-bladder. In the other form this insoluble compound of bilirubin forms the whole calculus. These stones are of small size—from that of a grain of sand to that of a pea—and form solid brownish-black concretions with rough, irregular surfaces; sometimes of wax-like consistence, sometimes firm, hard, and brittle. They consist almost entirely of the calcium compound of bilirubin or biliverdin, without any cholesterol, or at most with mere traces of it.

Besides these forms of calculi, in which it forms the chief constituent, bilirubin-calcium is a common constituent of most gall-stones, either intermixed with the cholesterol or sometimes forming the central nucleus.

A special interest attaches to these calculi of bilirubin-calcium; inasmuch as, unlike the ordinary mixed cholesterol calculi, the seat of the formation of which is the gall-bladder or very rarely the larger bile-ducts, small bilirubin-calcium calculi are frequently found in the intrahepatic ducts. What determines their formation? Both bilirubin and calcium are normal constituents of the bile. Yet in whatever amount they are present, or however highly the bile may be concentrated, they can never be made to combine to form this insoluble compound. Mere excess of bilirubin appears insufficient of itself to bring this about in normal bile. Addition of lime water, however, leads eventually to a precipitation of bilirubin-calcium. But certain substances in the bile appear capable of hindering this precipitation even when lime is present in abundance. The bile salts possess this power. Naunyn finds that in the presence of bile salts the calcium combines at first with the bile acid; and it is not until a large excess of lime is added that precipitation takes place. It is not likely that the precipitation of this compound is solely dependent upon an increase of lime in the bile. It is suggested that excess of lime in drinking-water may give rise to calculi by favouring the precipitation

of bilirubin-calcium ; there is no evidence, however, that the amount of lime in the bile is affected by the administration of lime in the food (Naunyn). Its source in all probability is the mucous membrane of the bile passages, as pointed out by Frerichs. More important than any mere increase of lime or amount of bile pigment in determining the precipitation of bilirubin-calcium is the presence or absence of albumin in the bile. Thus, egg albumin brings about a precipitation of bilirubin-calcium from bile, and from a solution of bile salt containing bilirubin. It is highly probable, then, as Naunyn says, that albumin is the chief factor in determining the precipitation of these biliary concretions within the bile-ducts, the albuminous material being derived from the desquamation and disintegration of the epithelium of the bile passages.

These small intrahepatic calculi of bilirubin-calcium seem to play an important part in producing cholelithiasis. They are carried into the gall-bladder, where they act on its mucous membrane as foreign bodies, and favour the catarrhal condition which leads to the formation of cholesterol. In the centre of gall-stones a small nucleus of this compound is frequently to be found.

The precipitation of bilirubin in insoluble form, with the production of biliary concretions of bilirubin-calcium, is thus to be regarded as evidence of disorder of the bile passages, not of the liver-cell itself.

(iv.) *Disturbances connected with Variations in Excretion of Bile Salts.*—We have little information as to the variations in their excretion met with in disease. Clinically our chief interest is directed to the bile salts in connexion, first, with their solvent action on cholesterol, the chief constituent of gall-stones ; and, secondly, with their appearance in the urine in cases of jaundice. Cholesterol is held in solution in the bile mainly by the presence of the bile salts ; it is insoluble in water or aqueous saline solutions, but easily soluble in solutions of the bile salts ; solutions containing $\frac{1}{4}$ to $2\frac{1}{2}$ per cent of bile salts can dissolve about a tenth part of their own mass of cholesterol (Naunyn). One of the oldest views of the origin of gall-stones is, that owing to decomposition of the bile acids within the gall-bladder, the cholesterol is no longer held in solution and becomes precipitated (Frerichs). There is no conclusive evidence, however, that calculi ever arise in this way. The evidence presently to be considered goes rather to shew that gall-stones arise from increased secretion of cholesterol from the walls of the gall-bladder, not from simple precipitation of the cholesterol held in solution.

Much importance was formerly attached to the presence of bile acids in the urine in certain cases of jaundice, and to their absence in others, as an important gauge of the degree of activity of the liver. Since the bile acids are admittedly formed by the liver, and by the liver alone, their absence from the urine, in any case of jaundice, was held to be due to inactivity of the liver. Hence the view of a haematogenous as distinct from a hepatogenous jaundice. This matter will be considered fully elsewhere (art. "Jaundice"). Here it can only be said that the studies of Stadelmann have thrown an entirely fresh light on this subject. So far

from the formation of bile pigments and of bile acids by the liver-cell necessarily going hand in hand, as hitherto assumed, these studies shew that a large increase of bile pigments in the bile is frequently attended with a no less marked diminution in bile acids. This peculiar result is especially characteristic of the action of certain poisons which possess powerful icterogenetic properties (toluylenediamine, phosphorus). The jaundice caused by such agents is always marked by a greatly diminished formation of bile acids; and hence at the very time the urine is loaded with bile pigment there may be little or no trace of bile acids.

(v.) *Disturbances connected with Excretion of Mucus and of Cholesterin.*—
Cholelithiasis.—The chief interest attaching to cholesterin is that it forms the chief constituent of gall-stones. With regard to its source there is still difference of opinion. Its widespread distribution within the body would suggest that it is excreted by the liver. In cases of jaundice with complete obstruction it is said to accumulate in the blood (Frerichs), but this statement lacks confirmation. It is now known that it is not merely excreted from the blood, but that it is formed by the mucous lining of the gall-bladder and the larger bile-ducts (Naunyn), and that it is really a product of degeneration of the epithelium of their coats. According to Naunyn, cholesterin is not simply excreted by the liver, for he found no noteworthy increase in the bile after administration of large quantities of cholesterin, both by the mouth and subcutaneously; he concludes, indeed, that no separation whatever of cholesterin from the blood takes place through the bile. He finds, moreover, that the amount of cholesterin is not dependent upon diet. He also investigated the excretion of cholesterin in various diseases, but failed to find any notable increase of the substance, unless gall-stones were also present. He concludes, then, that the cholesterin of the bile is neither a product of general metabolism nor a specific secretion product of the liver.

On the other hand, the secretion of mucous membranes constantly contains cholesterin, sometimes in no less quantity than the bile itself. In bile the proportion varies from 0·5 to 3·5 per 1000. In sputum of catarrhal bronchitis Naunyn found it to the amount of 0·9 in 1000, and in sputum of putrid bronchitis he found it to the amount of 1·5 per 1000. In pus it has been found in even higher amounts. In all these cases there has been actual inflammation and an abnormally large amount of degeneration of cells and epithelium; and Naunyn thinks it probable that a considerable shedding of epithelium from the biliary passages, induced by the deleterious action of the bile itself (as a protoplasmic poison), constantly goes on. An increased formation of cholesterin in connexion with subacute inflammatory and catarrhal conditions of the lining membrane of the bile passages, especially of the gall-bladder, is the chief factor underlying the formation of gall-stones in disease. The cholesterin which goes to form gall-stones has never been in solution in the bile. It is formed as viscous material within the degenerated epithelium thrown off from the gall-bladder; and it collects, as such, either

around amorphous particles made up of degenerated epithelium, or around small solid concretions of bilirubin-calcium. Once formed, the calculus grows by further accretion either of cholesterol or bilirubin-calcium, or both. The cholesterol, according to Naunyn, may accumulate in two further ways ; it may come either from degeneration of the epithelium lying around it, as in the cases in which a stone lies in a pocket embracing it so closely that no bile may have entered for some time ; or, on the other hand, when the stone is bathed in bile, it may grow by crystallisation of the cholesterol in the bile. But this mode of increase is rare. In the great majority of calculi the superficial layer is not crystalline, but at first is amorphous ; it is at a subsequent date that this amorphous cholesterol undergoes crystallisation.

What is it that determines this increased formation of cholesterol ?

The facts with regard to the general etiology of gall-stones are well known (*vide p. 252*). Gall-stones are uncommon in young people under thirty years, and most common over sixty. They are much commoner in women than men—among males in 4·4 per cent of bodies examined, among women in 20·6 per cent. Among women they are much more frequent in those who have borne children. Thus it appears that the formation of gall-stones is facilitated by anything which interferes with or retards the flow of bile. Stagnation of bile is an etiological factor about which there is no dispute.

How, then, does stagnation of bile lead to the formation of biliary calculi ? Frerichs taught that in stagnating bile the bile salts were apt to undergo decomposition, the reaction of the bile to become acid, and the cholesterol, previously held in solution by the bile salts, to be precipitated. It has, however, been proved that stagnation alone is not sufficient to give rise to the formation of gall-stones (Mignot). Naunyn has shewn that for the production of cholesterol in excess, and so of calculi, a catarrhal condition of the mucosa is necessary, and it is clear that the etiological importance of biliary stagnation consists in its favouring infection and catarrh of the gall-bladder. The catarrh responsible for the increase of cholesterol, and so for the formation of calculi, may be induced by two sets of factors : (1) Non-infective and (2) Infective. The non-infective factors include the effects on the bile passages of irritant products of digestion, insufficiently metabolised and detoxicated by the liver, and excreted into the bile. The latter include the effects of bacterial toxins, either absorbed from the intestine (icterogenous toxins) or formed within the infected gall-bladder. (For the bacteriology of cholelithiasis *vide p. 254*.)

Conclusion.—Thus it appears that the large group of morbid conditions comprised under cholelithiasis are due to catarrh of the bile passages set up by the excretion of irritant poisons through the bile, or by the formation of such poisons by infection of the gall-bladder.

F. The disturbances of digestive functions associated with functional hepatic insufficiency are both numerous and varied. They include many of the commonest manifestations of gastro-intestinal

disturbance—the coated tongue, bitter taste in the mouth, loss of appetite, acidity, flatulent distension, distaste for food, especially those of fatty nature, sense of discomfort or actual soreness in the stomach and duodenum, "biliaryness" of every degree of intensity from conjunctival jaundice up to complete jaundice, constipation with deficiency of bile in the stools, or looseness of bowels with excess of bile in the stools, deposits of urates in the urine. As already seen (p. 43) these gastro-intestinal disturbances are in most cases as much the cause as the effect of the liver disturbances associated with them, and this is specially true of the biliary disorders. But these latter in their turn undoubtedly aggravate the gastro-intestinal disturbances in certain directions. Thus, stagnation of bile reacts upon the secretion of gastric juice—leads to its increase and to consequent hyperacidity. Deficiency or absence of bile from the intestine affects the motor activity of the bowel—diminishing it—and thus favouring constipation. It does not interfere much with the assimilation of the carbohydrates or proteins of the food, for on these the bile exerts practically no action. On the other hand the reabsorption of fat is greatly impaired, for the bile not only emulsifies fats, but it also removes the fatty acids and soluble soaps, and stimulates the epithelial cells to absorb them. When bile is cut off from the intestine, the faeces contain a large excess of fat; instead of containing only about 6 per cent of the fat administered, the amount thus lost may be as much as 55 to 78 per cent. It is the presence of this fat which gives the peculiar clay colour to the faeces in obstructive jaundice; it may constitute as much as 11 to 13 per cent of the weight of the faeces. It may be in part responsible for the peculiar sickening fetor which faeces free from bile usually have; but Dr. Gamgee has observed the complete absence of fetor, in spite of large quantities of unabsorbed fat, in cases of fatty stools due to disease of the pancreas without pressure on the common bile-duct. It is certain, however, that if dogs with biliary fistula be fed on carbohydrates instead of fat, the fetor in great part disappears. This peculiar fetor of the faeces in the absence of bile has led to the view that the bile has powerful antiseptic properties. It certainly has no direct antiseptic action, for micro-organisms of various kinds grow freely in media containing bile and in the bile itself (Copeman and Winston, Sherrington). On the other hand, free bile acids have antiseptic properties. It is probable that as soon as the bile comes into slight contact with the intestinal contents, the bile salts are decomposed, and bile acids set free; and it has been suggested (Gamgee) that the presence of these acids may modify in some way the putrefactive changes which albuminous substances undergo in the intestine. The most recent observations, however, shew that the peculiar colour is not due to putrefactive fermentation, as has generally been supposed. The total bulk of bacteria in the faeces is not increased, but on the contrary remarkably diminished (Strasburger, 1903). The peculiar fetor is thus probably due to excess of fatty acids. In some cases even this is absent. In the case of biliary fistula recorded

by Mr. Mayo Robson, in which for fifteen months all bile was discharged externally, the odour of the faeces did not differ from that of a healthy motion, and the bowels were quite regular throughout without the use of aperients. Although nutrition is usually affected by the loss of the fats of the food (hence the wasting of chronic jaundice), even this effect is absent in some cases. In the case of biliary fistula recorded by Professor Noel Paton, the woman returned after a year's interval in a state of robust health, having put on a stone in weight notwithstanding the complete absence of bile from the intestine.

Apart from these obvious effects (on fat absorption, on intestinal peristalsis, on nutrition), absence or deficiency of bile also causes effects of a less obvious but probably no less important character. Although the bile has no direct antiseptic properties, it appears to have antitoxic powers of no mean order (T. R. Fraser, 1897) by which it can antagonise and render inert powerful organic poisons, such as those of snakes. There are many poisonous products generated in the intestine, in connexion with pancreatic digestion and intestinal putrefaction, capable if absorbed of producing ill-effects. Some of the symptoms commonly ascribed to "sluggish liver" or "want of bile" may be due in part at least to the absence of a sufficient amount of healthy bile, and consequent absorption of products that would otherwise have been rendered inert by it. The undoubted value of cholagogue substances—"stimulants of bile secretion"—so long employed on clinical grounds alone may thus obtain a satisfactory explanation. Absence or deficiency of bile may affect the functions of the liver in another way. All experimental evidence goes to shew that no drug is so powerful a stimulant of bile secretion as the bile acids formed by the liver itself, and constantly reabsorbed in large quantity from the intestine. In cases of jaundice (p. 75), the formation of bile acids is, in consequence of the absence of this secondary circulation, much diminished and the proteolytic function of the liver in this respect materially affected.

In all these ways, then, by diminished absorption of fat, by diminished peristalsis, by diminished antitoxic power of the bile on the food products within the intestine, by diminished absorption of bile salts, all the functions of the liver—proteolytic, glycogenetic, biliary, and antitoxic—may be affected by the intestinal changes connected with defective secretion of bile.

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For other references see art. "Jaundice."

W. H.

JAUNDICE

By WILLIAM HUNTER, M.D., F.R.C.P.

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Definition. — A general condition symptomatic of obstruction of the bile-ducts alone (hepatogenous jaundice), or in association with toxæmia and infection (haemo-hepatogenous jaundice); characterised by yellowish discolouration of the tissues with bile pigment, the excretion of bile pigments in the urine with or without bile acids; and by various general symptoms referable, in simple cases, to disturbances of gastro-intestinal and liver functions; in more severe cases, to disorder of the blood as well as of the liver (fever, cerebral symptoms, haemorrhages); caused by absorption of bile from the bile passages as the result of impeded outflow.

CAUSES OF JAUNDICE

All cases of jaundice may be classed in two great divisions:—

I. Jaundice resulting from obvious mechanical obstruction independent of changes in the blood or bile (Simple Obstructive Jaundice).

II. Jaundice dependent upon changes in the blood and bile; the actual cause of obstruction being increased viscosity of bile, consequent on intrahepatic catarrh (Toxaemic Obstructive Jaundice).

I. SIMPLE OBSTRUCTIVE JAUNDICE

The causes may be grouped as follows:—

A. Obstruction by Pressure on the Ducts from without:—

(a) *Obstruction by Tumours pressing on the Cavity of the Ducts, or growing into their Interior.*

1. Tumours projecting from the liver. 2. Enlarged glands in the fissure of the liver. 3. Malignant disease of the stomach. 4. Malignant disease of the duodenum. 5. Malignant disease of the pancreas. 6. Tumour or displacement of the kidney. 7. Retroperitoneal or omental tumour. 8. An abdominal aneurysm. 9. Faecal accumulation. 10. A pregnant uterus. 11. Ovarian and uterine tumours.

(b) *Obstruction by Inflammatory and Cicatricial Processes in parts adjacent to the Bile-ducts.*

1. Duodenitis and cicatrisation of duodenal ulcers. 2. Peri-hepatitis. 3. Chronic pericholecystitis and pericholangitis. 4. Acute and Chronic pancreatitis. 5. Cirrhosis of liver.

(c) *Obstruction by Congenital or Spasmodic Conditions.*

1. Congenital deficiency or stenosis of the bile-duct. 2. (?) Spasmodic stricture.

B. Obstruction by Morbid Processes in the Walls of the Ducts.

(a) *Cholangitis* of every degree of severity; caused by—1. Congestions. 2. Excretion of irritant digestive products through the bile. 3. Very frequently by infection, occasioning an increased formation of viscid mucus, which impedes the flow of bile or may arrest it altogether, and leads to the formation of biliary sand and calculi; affecting every part of the biliary system. This catarrh is by far the commonest cause of jaundice.

(b) *Malignant Disease and Stricture of the Bile-ducts.*

C. *Obstruction in the Cavity of the Ducts.*—(1) *Biliary Sand and Calculi*—formed chiefly in the gall-bladder,—a common cause of jaundice, both by exciting catarrh, and by occasioning mechanical obstruction when the gall-stones reach the common bile-duct; and by disposing to infection and to carcinoma of the biliary system; (2) *mucus*; (3) *worms*.

For the symptoms, morbid anatomy, differential diagnosis, and treatment of the several varieties of jaundice caused by mechanical obstruction, the reader is referred to the various articles dealing fully with the different causes of this condition, as detailed in the foregoing list, namely—

1. Functional disturbances of biliary secretion (p. 50).
2. Inflammatory affections of gall-bladder and bile-ducts (p. 223).
3. Tumours of the gall-bladder and bile-ducts (p. 242).
4. Gall-stones (p. 251).
5. Tumours of the liver (p. 204).
6. Congenital obliteration of the bile-ducts (p. 103).
7. Cirrhosis of the liver (p. 169).
8. Congestion of the liver (p. 155).
9. Tumours of the pancreas (p. 303).

II. TOXAEMIC OBSTRUCTIVE JAUNDICE

SYNONYMS.—*Haemo-hepatogenous jaundice* (Afanassiew); *Jaundice of polychromia* (Stadelmann); *Non-obstructive jaundice, Toxaemic jaundice* (Hunter).

Definition.—A form of jaundice connected with disorder of the blood, met with in a number of conditions; sometimes as a complication of specific febrile conditions, sometimes as the prominent feature of conditions of obscure, probably infective, nature: it is *characterised* by jaundice of varying severity in association with symptoms of more or less general disturbance; in severe cases by fever, delirium, epistaxis, black vomit, albuminuria, and other symptoms of blood disorder: it is *caused* by the agency of various organic poisons, acting on the blood first and subsequently excreted through the liver, leading to altered character and viscosity of the bile, and in severe cases to degenerative changes in the liver-cells.

Varieties.—The varieties of jaundice falling within the scope of the above definition may be grouped in four classes, according to their etiology—

1. Jaundice produced by the action of *chemical poisons*, such as toluylenediamine, phosphorus, arsenic, snake-bite.
2. Jaundice due to poisons formed in the various forms of gastro-intestinal auto-intoxication.
3. Jaundice due to the poisons formed in various specific fevers and conditions, such as yellow fever, malaria, pyaemia, relapsing fever, typhus, enteric, and scarlet fever.

4. Jaundice met with in various conditions of unknown but more or less obscure infective nature, and variously designated as epidemic, infectious, febrile, malignant jaundice, icterus gravis, Weil's disease, acute yellow atrophy of liver.

A. GENERAL CHARACTERS

Although differing widely from one another in severity and in individual character, there are certain general characters common to all these forms of jaundice which mark them off as a distinct group, conveniently described as *toxaemic*.

(1) *Pathological Features*.—In all of them the jaundice appears to be independent of any obstruction to the flow of bile, or at any rate no obvious obstruction can be found in the larger ducts. In all of them the jaundice is associated at one time or other with the presence of more or less bile in the stools, sometimes indeed with an excess of bile (*poly-cholia*). In all of them bile acids are not present in such quantity in the urine as in cases of jaundice of purely obstructive nature; they may indeed be absent altogether—a point of difference to which, following Leyden's original teaching, it has been customary to attach a significance altogether out of proportion to its importance.

We now know from Stadelmann's studies that in all these respects the jaundice met with in disease agrees in its characters with that produced by drugs like phosphorus or toluylenediamine, so closely indeed as to leave no room for doubt that in disease poisons are also at work. In particular a diminished formation of bile acids appears to be a feature of the action of all such agents—even when causing a largely increased formation of bile pigments; so that their absence from the urine or their presence in diminished quantity in these cases is thus satisfactorily accounted for. And so with regard to the presence of bile in the stools—the action of all these *icterogenetic* drugs is attended at one stage or other by increased formation of bile pigments and increased flow of bile.

Clinical Features.—The jaundice in the foregoing class of cases presents certain general points of resemblance distinguishing it from the jaundice of purely obstructive origin. In the first place, the jaundice is usually less intense in its character than that met with in obstruction, being frequently evidenced by a slight yellowish or greenish-yellow discolouration of skin and conjunctivae rather than the deep golden yellow or green colour of obstructive jaundice. It appears to be due, as indeed it is, to the absorption of some, rather than to the complete retention of the bile pigment formed. But whilst this is its character in general, it may, on the other hand, be as intense as the jaundice of pure obstruction. Of this nature is the jaundice of toluylenediamine poisoning. In severe cases it is as complete and intense as if a ligature had been applied around the bile-duct; but it is only for the time being, for another feature of the jaundice thus caused is that it is of a more

temporary character than that caused by mechanical obstruction. It passes off with the condition of blood and bile on which it depends ; that is, in the case of jaundice of drugs, as soon as the action of the poison has exhausted itself.

In the second place, this variety of jaundice is generally associated with more constitutional disturbance than is the case with ordinary obstructive jaundice. The mildest forms of toxæmic jaundice, occurring in the course of an epidemic outbreak, and obviously, therefore, the result of some more or less infective influence, may not be distinguishable from cases of ordinary "catarrhal" jaundice of duodenal origin, and may present little constitutional disturbance, if any.

But some degree of general disturbance is usually present, and in the severe cases this is so pronounced—dry tongue, fever, delirium, subsultus, convulsions, epistaxis, black vomit, diminished excretion of urine, and albuminuria,—symptoms of the "typhoid state,"—that the jaundice becomes one symptom only of a general condition of severe poisoning. Moreover, although the symptoms vary very greatly in their intensity in different classes of cases, they have the same general character. At first sight it might appear necessary to distinguish between the form of jaundice accompanying definite specific fevers, such as malaria, yellow fever, typhoid fever, and the like, and that met with apparently as an independent affection in epidemic, febrile, infectious, malignant jaundice, Weil's disease, acute yellow atrophy of liver. And still more might it appear necessary to distinguish in this last group of cases between forms apparently so widely diverse as mild cases of catarrhal (epidemic) jaundice and severe cases of Weil's disease, malignant jaundice, and cases of that rare disease, acute yellow atrophy. But in reality, both from a clinical and a pathological point of view, they all present certain features in which they resemble each other, and no sharp line of distinction can be drawn betwixt them.

The severest cases of an outbreak of catarrhal (epidemic) jaundice may be marked by so much fever and constitutional disturbance as to be indistinguishable from cases of what is variously called icterus gravis, febrile, infectious, or malignant jaundice. Similarly, Weil's disease differs in no respect from forms of icterus gravis described long ago by many observers—Graves and others. And lastly, as I shall presently have occasion to shew, it is sometimes difficult to draw any clear line of demarcation between the severest forms of icterus gravis, or chloroform poisoning, and acute yellow atrophy of the liver. In mode of onset, character of symptoms, progress of case, and lastly, in character of post-mortem appearances, cases have been observed and recorded as occurring in the course of endemic outbreaks of jaundice which were not to be distinguished from acute yellow atrophy of the liver, even in the minutest particulars supposed to be characteristic of the latter disease ; such as atrophy of the liver, diminished excretion of urea, and the discovery of tyrosine and leucine in the urine and liver. So far, indeed, as the last-mentioned points are concerned, identical changes—yellow atrophy of the liver,

presence of leucine and tyrosine in the liver and in the urine, diminished excretion of urea—have been found by Frerichs, Murchison, and others in severe cases of jaundice occurring in typhus, enteric, and relapsing fevers.

It thus appears that even in their clinical features all these forms of jaundice have a good deal in common. Their symptoms have a generic likeness, from the initial jaundice, with or without general disturbance, common to all alike, to the marked cerebral and toxic phenomena which characterise the severest cases. The differences in character manifested by the special forms are doubtless due to differences in the character and intensity of the poisons. The differences observable in the action of such agents as phosphorus, arseniuretted hydrogen, toluylenediamine, chloroform, shew that the power of inducing jaundice (icterogenetic power) is possessed by poisons in very varying degree.

But whatever the character of the other symptoms, the icterogenetic power is usually associated with three classes of changes—(a) destructive changes in the blood; (b) alterations in the quantity and quality of the bile; (c) marked functional or parenchymatous changes in the liver-cells, and, as the case of toluylenediamine illustrates, in the bile-ducts, and also in the renal cells. In disease all these modes of action are manifested in varying degree, especially in severe cases; the degree of blood change being frequently shewn by marked haemolysis, the occurrence of bleedings from nose and stomach (black vomit). According to Chauffard (1908) the blood in simple obstructive jaundice shews increased resistance to haemolysis and the red corpuscles are larger in size; in toxæmic jaundice, on the other hand, there is "fragility," or a great liability to haemolysis, the corpuscles are smaller and shew granular degeneration. The action on the liver and kidneys is shewn by the occurrence of extensive parenchymatous changes in both organs.

Etiology.—As regards their etiology the above cases have a good deal in common. Their etiology, except in the first class, in which we have to deal with the action of definite poisons, such as phosphorus or chloroform, is obscure. Age, sex, occupation, habits of life are without any definite influence of themselves, except in so far as they favour the incidence and the toxic effect of the infection occasioning them. For it is to this latter mode of origin that the preponderance of evidence points, even in the isolated (sporadic) cases. This infective character becomes most manifest when, as not infrequently happens, the jaundice assumes an endemic or even epidemic character, affecting those in the same household or district, or spreading over larger areas. But the resemblance between the severe cases met with in such circumstances and the isolated cases—for example, *icterus gravis*—in which no definite infection can be proved, suggests very strongly that these latter also have an infective origin.

In a number of such cases, indeed, organisms, of varying character have been described as occurring in the liver. Of the nature of the infection nothing definite is known. There is hardly any reason, however,

to doubt its microbic origin ; and it is exceedingly probable that it is of very varying character—that the power of forming poisons, possessing more or less icterogenous properties, is one possessed by a number of different organisms. But the comparative rarity of forms of infective jaundice indicates that the power is not one possessed by the ordinary microbes inhabiting the intestinal tract. Moreover, the comparative rarity with which jaundice of this kind is met with, complicating marked infective conditions of the intestinal tract, speaks to the same effect. Thus, jaundice is of very rare occurrence in enteric fever.

We may take it then, I think, that in these forms of jaundice we have to do with the action of organisms of specific nature, whether of a bacterial or other kind remains still to be shewn ; organisms of varying character and virulence ; limited in their distribution, or even rare, in this country and in temperate climates, but more widely distributed in tropical climes (for example, the infection of yellow fever, of malarious disease, and the remarkably endemic character of outbreaks of jaundice in some parts of Southern Australia).

The seat of infection in most cases is probably the intestinal tract. Intestinal symptoms—for example, diarrhoea, more or less fetid in character—form a prominent feature of a large number of such cases at the outset of the illness. It is extremely likely that in the largest number of cases the infection remains confined to this tract, and does not spread to the blood ; the action on the blood is limited to the poisons absorbed.

B. PATHOLOGY OF TOXAEMIC JAUNDICE

(a) **Historical Hypotheses of Jaundice.**—That jaundice does arise in connexion with certain disorders of the blood is a very old observation. The connexion of the two disorders is indeed frequently referred to as far back as the time of Galen ; but such observations indicate little more than the prevailing opinion of ancient writers that disorder of the blood is the primary cause of most diseases.

I. The Suppression Hypothesis.—According to this hypothesis the jaundice, unattended by obstruction, is due to a suppression of the biliary secretion as the result of some morbid action of the liver itself. "The biliary ingredients are not eliminated, and consequently accumulate in the blood." This is the oldest conception of all. At what time, indeed, it took origin is not clear. A doctrine identical with it was expressed by Boerhaave (1709) and by Morgagni ; but it is probably much older than their writings. Such a doctrine was in strictest keeping with the early knowledge of the functions of the liver, its chief function being compared to that of a sieve which strains off the bile from the portal blood (Glisson, 1659).

According to the modern version of this hypothesis, biliary secretion can be retarded or even totally arrested, for instance by nervous influence, without any structural alterations in the liver-cell. The liver can "strike work" and refuse to secrete bile, and the result is jaundice. It is claimed for this hypothesis that it rests on a basis of pathological data, and in support of its accuracy special

importance is attached to certain cases of obstruction described by Moxon and others, in which the gall-bladder and larger bile-ducts behind the point of obstruction are found filled with colourless mucus free from all trace of bile.

The class of cases to which it is applied by its supporters includes—
(i.) Those in which jaundice occurs as the result of sudden mental emotion or other severe nervous disturbance ; (ii.) Most of the cases in which it occurs in connexion with disorder of the blood, such as typhus, enteric fever and infective diseases generally, icterus gravis, yellow fever, acute yellow atrophy, snake poisoning and phosphorus poisoning—cases of much the same class, indeed, as those to which the haematoxenous doctrine applies. And, indeed, at some points the two doctrines are closely related. They differ, it is true, in this respect, that whilst according to the haematoxenous doctrine the whole fault lies with the blood, the only fault ascribed to the liver being that it cannot dispose of all the haemoglobin supplied to it ; according to the suppression hypothesis, on the other hand, the fault lies entirely with the liver, the function of which is arrested. Nevertheless the two views have this in common, that both assume the bile pigments to be formed from haemoglobin within the blood, and merely to be excreted by the liver ; and, consequently, that jaundice is liable to occur if at any time there be an excess of haemoglobin in the blood on the one hand (haematoxenous), or an arrested activity of the liver on the other (suppression hypothesis). In disease, as it happens, both factors are often combined, since the poison which acts injuriously on the blood also acts injuriously on the liver. Hence it is impossible to separate the two processes entirely ; since, but for the facts in support of the haematoxenous doctrine, the conception of suppression would have little or nothing to recommend it.

The conception of jaundice by suppression received support from Andral (1829), Budd (1845), Sir Thomas Watson (1867), Bamberger (1857), Troussseau (1865), Liebermeister (1864), Harley (1880), and Moxon (1873). The last-named observer, indeed, went so far as to apply it to obstructive forms of jaundice no less than to those in which no obvious obstruction could be found. In obstructive jaundice he considered the yellowness to be caused by suppression of the secretion, and not by absorption of bile already formed ; unless as an unimportant incident of the earlier stages of the jaundice, "We may deny that reabsorption of bile is a cause of jaundice." In extending the doctrine of suppression thus far, Moxon, I think, stands alone ; its other supporters are content to apply it to the cases in which no obvious obstruction can be found. The view that jaundice may arise by suppression has remained the most permanent of all the older hypotheses of jaundice. In some form or other it is still held by some to apply to certain forms of jaundice, more especially those connected with mental emotion.

II. Jaundice from Redundant Secretion (Polycholia).—Towards the end of the eighteenth and at the beginning of the nineteenth century it is to be noted that the chief authors discuss the possibility of a form of jaundice unconnected with obstruction in the liver, though they are very far from admitting its probability. It is clear, however, that the jaundice connected with blood disorder was clinically well known to them. Thus, Reil (1782) gave a long description of its chief features under the title polycholia, with rules for distinguishing it from ordinary jaundice. Saunders also (1809) recognised that jaundice might be associated with a redundant secretion of bile and be independent of biliary obstruction, as, for example, the jaundice of yellow fever. He even

went so far as to admit that in certain morbid states the blood might acquire a bilious appearance independently of absorption or regurgitation of bile from the liver, thus practically anticipating the later haematoogenous doctrine of jaundice. But he held such a mode of origin of jaundice to be unlikely. "In every case of jaundice bile must be secreted and carried into the blood-vessels"; in other words, the jaundice is essentially of obstructive origin. He was the first to demonstrate by experiment the channels by which, after obstruction of the bile-duct, the absorption of bile takes place; namely, the lymphatics. He ligatured the bile-duct, and afterwards was able to trace the lymphatics of the liver distended with bile up to their junction with the thoracic duct.

Still later (1827) Cullen also rejected any other mode of origin of jaundice than that of absorption of bile already formed by the liver. He distinguished two ways in which jaundice might arise in this way, namely: (i.) obstruction to the flow of bile into the duodenum; and (ii.) reabsorption of bile from the alimentary canal when it had accumulated there in an unusually large quantity. How far this accumulation could take place, and in what circumstances it occurs, he could not clearly ascertain; he considered, however, that jaundice was seldom produced in this way.

Similarly most other writers about the end of the eighteenth century taught that the doctrine of jaundice from absorption was the only trustworthy one; jaundice was essentially obstructive in its nature. And it may be stated generally that, up to the end of the first quarter of the last century, the state of knowledge did not permit any further deduction. It was recognised that there are certain forms of jaundice not clearly traceable to obstruction, but difficult to account for on any other supposition.

III. Frerichs' Hypothesis.—During the second quarter of the last century the view, hinted at by Saunders, that jaundice might arise from pure disorder of the blood, independently of obstruction, began to take more definite form. It was not, however, till 1858 that any serious attempt was made to define more precisely what such a view implied—to indicate whether the fault lay in the blood or in the liver. The first attempt of this kind we owe to Frerichs, whose results appeared to shew that the fault lay in the blood, and that the jaundice was due to accumulation of bile pigments imperfectly oxidised in the blood.

Frerichs distinguished two possible causes which might lead to an accumulation of bile constituents in the blood: (i.) increased absorption of bile into the blood, either from obstruction in the bile-ducts, or from abnormal diffusion of bile into the blood capillaries of the liver under conditions in which the blood-pressure within the liver was diminished; or (ii.) diminished consumption or metamorphosis of the bile constituents absorbed into the blood in normal circumstances from the alimentary canal. Chief among these constituents and the precursors of the bile pigments he considered to be the bile acids; for he found that, by the action of sulphuric acid on bile acids, various pigments or chromogens were formed resembling in many respects the pigments of the bile, especially in their behaviour towards Gmelin's test. On the basis of these observations he conceived the normal fate of the bile acids absorbed from the intestine into the blood to be that they underwent a similar change in the blood, and were converted into bile pigment; and that this in turn became oxidised within the blood into urinary pigment. Any interference with this normal oxidising process would thus necessarily lead to an excess of bile pigment in the

blood ; and in this way a jaundice might arise quite independently of any obstruction. Frerichs made certain other observations which seemed strongly to support his opinions. For he found that if bile salts were injected into the blood of dogs they disappeared, while bile pigment appeared in the urine. According to this view, then, the fault lay entirely with the blood, which did not oxidise the bile pigment normally absorbed into it ; and jaundice might arise either from increased absorption of bile into the blood, or from diminished metamorphosis of bile absorbed in normal quantity.

IV. KÜHNE'S HYPOTHESIS.—"Haematogenous Jaundice."—Frerichs' important observations on the appearance of bile pigment in the urine after the injection of bile salts into the blood were soon confirmed by Kühne (1858). But so far from lending support to the views of Frerichs, Kühne's observations led, curiously enough, to the establishment of a radically different conception of jaundice. Kühne found that if, instead of bile salts, he injected haemoglobin into the blood, bile pigment still appeared in the urine. He concluded, therefore, that the bile acids did not become directly converted into bile pigment, as Frerichs had supposed, but that they liberated the haemoglobin of the corpuscles, and that this was subsequently transformed into the bile pigment. On the ground of these observations he formulated the doctrine that all agents capable of liberating an excess of haemoglobin in the blood were capable of inducing icterus—at any rate to a degree sufficient to cause bile pigment to appear in the urine. The important point established by Kühne was that haemoglobin is the source of the bile pigments. This observation marked a new era in the history of the subject ; later observations have but confirmed its truth. Very soon it received support from Virchow's discovery in and around old extravasations of blood of crystals of haematoidin—a pigment closely resembling bilirubin if not identical with it. As the haemoglobin of extravasated blood could undergo this conversion, it was reasonable to suppose that in certain circumstances it might undergo a like transformation in the blood. Taken with the foregoing observation that bile pigment appears in the urine after the injection of haemoglobin into the circulation or on its liberation there, the evidence seemed, indeed, conclusive that such a transformation had taken place, and this, too, directly in blood without the intermediation of the liver. The liver was not concerned in the process. Such jaundice must be purely "haematogenous"—in no sense obstructive.

The doctrine of a haematogenous jaundice thus formulated very soon received what appeared to be strong support from the clinical side. Leyden's important observations (1866) appeared to confirm the view that the blood, and not the liver, is the tissue at fault. He found that in obstructive jaundice bile acids are always present in the urine with bile pigment; whereas in the jaundice of pyaemia and allied blood disorders they are not to be found. As the bile acids are formed by the liver, their absence from the urine in such cases seemed to indicate inaction of the liver and that the bile pigments present in the urine had not been formed by the liver, and, consequently, that this jaundice is not due to obstruction.

As a matter of fact the accuracy of Leyden's observation was very soon called in question. But it fitted in so completely with Kühne's doctrine that his teaching soon gained a very general acceptance, and has held its ground even up to recent times. The detection of bile acids in the urine has been accepted as a sign of obstructive jaundice, their absence as a sign of so-called non-obstructive or haematogenous jaundice. The chief supporters of the

doctrine of a haematogenous jaundice at various times have been Leyden in Germany, Gubler in France (1857), Budd (1845), Harley, Bristowe (1890), and Fagge in this country.

The class of diseases to which it was held to apply were such as pyaemia, enteric fever, pneumonia, and febrile jaundice generally ; the jaundice following burns and the injection of water, pyrogallic acid, or other destructive agents into the blood ; and that of malaria, paroxysmal haemoglobinuria, and other diseases marked by haemolysis.

The doctrine always failed, however, to gain acceptance from Frerichs in Germany, Murchison, and Wickham Legg. It was indeed very soon rejected as insufficient by Virchow, who was the first to suggest the name haematogenous to describe this kind of jaundice ; and, as we have seen, his own observations lent no little support to the doctrine. Yet, whatever his early views, his later opinion undoubtedly was that a purely haematogenous origin of jaundice in any form is extremely improbable. Even in such diseases as pyaemia or pneumonia he held that obstruction, due, it may be, to catarrh of the bile-ducts, plays a very prominent part. It will presently be seen how fully this scepticism of the great pathologist has been justified by the most recent work on the subject.

Consideration of Foregoing Doctrines.—Of the four doctrines just considered, the only one which has contributed definitely to our knowledge is the haematogenous doctrine.

The suppression doctrine took origin at a time when the excretion of bile was supposed to be the sole function of the liver. In this case, if the liver cease to act, the bile constituents accumulate in the blood. We now know that the chief constituents of the bile do not pre-exist in the blood, but are formed by the liver.

Frerichs' teaching has contributed nothing. The bile pigments are not derived from bile acids as he supposed ; and the oxidation processes, to the arrest whereof the accumulation of bile constituents in the blood was ascribed, have as problematical an existence now as ever they had.

The haematogenous doctrine, on the other hand, is based upon a fact of definite importance, namely, that the bile pigments are derived from haemoglobin, and not infrequently appear in the urine after liberation of haemoglobin in excess. Where this doctrine proved wanting was not in data, but in the interpretation of them. It assumed that the conversion of haemoglobin into bile pigment takes place within the blood, and upon this assumption the doctrine depended. Indeed, the occurrence of jaundice in connexion with increased blood-destruction was conversely adduced by the physiologist as an argument in favour of the purely haematogenous origin of bile pigment.

So far as the haematogenous doctrine of jaundice is based on the possibility of the formation of bile pigments, or allied coloured derivatives of haemoglobin, directly from haemoglobin without the agency of the liver-cells proper, some basis for this doctrine still remains.

The Liver the Chief Seat of Formation of Bile Pigment.—On the other hand, so far as it rests on the assumptions that the bile pigments are normally formed within the blood, and that the liver merely excretes the

bile pigment conveyed to it, the haematogenous doctrine I consider to have been deprived by later observations of all basis whatever. For the important experiments of Stern on pigeons (1885), and of Minkowski and Naunyn on geese (1886), have conclusively shewn, for warm-blooded animals, what Kunde and Moleschott's experiments long ago shewed for the cold-blooded (frogs), that the removal of the liver under the precise conditions which ought to favour a haematogenous jaundice is not followed by jaundice at all. These observers shewed that, if in the healthy goose a liberation of haemoglobin be induced by the inhalation of arseniuretted hydrogen, bile pigments appear in quantity in the urine; without any free haemoglobin unless the destruction be great. If, however (under similar conditions), the liver be cut off from the circulation, either by excision or by ligature of all its vessels, the haemoglobin appears directly in the urine without any bile pigments. In the absence of the liver the haemoglobin is not converted into bile pigment as was the case in health. If the bile pigments were normally formed from free haemoglobin within the blood, the removal of the liver ought not to have appreciably affected their formation; still less should their formation be practically arrested. These results warrant the conclusion that, in normal circumstances, it is within the liver, not within the blood, that haemoglobin is converted into bile pigment.

The basis of facts on which the haematogenous doctrine rests is thus narrowed almost to vanishing-point. The only basis it retains is the somewhat slender one supplied by the observations above cited, namely, that the formation of haematoidin from haemoglobin is a purely chemical process independent of cell activity. On the ground of this observation Neumann and Löwit remain firm supporters of the haematogenous doctrine of jaundice. Slender as its basis admittedly is, this doctrine would nevertheless remain the most reasonable explanation to be offered of the obscure forms of jaundice connected with blood disorder, but for another series of observations, throwing an entirely fresh light on the whole subject, that have next to be considered.

(b) CONSIDERATION OF THE FACTORS CONCERNED IN THE PRODUCTION OF TOXAEMIC JAUNDICE.—(I.) Jaundice produced by Poisons.—*Stadelmann's observations—Haemohepatogenous jaundice.*—The observations referred to are those of Stadelmann (1881-1883). They shew, for the group of cases to which the haematogenous doctrine was supposed specially to apply, cases, that is, of jaundice accompanying an increased destruction of blood, that the jaundice is due to obstruction caused by well-marked changes in the character and consistency of the bile.

. *The Action of Drugs.*—The study of one drug in particular, tolulylenediamine, has proved of special interest in this relation. This drug, when injected into dogs, possesses the peculiar action, first noted by Schmiedeberg, of causing intense jaundice. Stadelmann, at the request of Schmiedeberg, undertook its closer study. He found that its action caused well-marked changes in the bile, differing at different stages. In the first stage

(beginning about two hours after the injection, and lasting twelve hours) the bile is increased in quantity and very rich in bile pigments. In the second stage (beginning about the fourteenth hour and lasting sixty to seventy hours) it becomes greatly diminished in quantity, gradually loses all the characters of bile, and assumes those of an extremely viscid colourless mucus. At the end of this time it begins gradually to assume its normal character, and there is again an increased excretion of bile pigments. The jaundice begins towards the end of the first stage, becomes very pronounced during the second, and gradually passes off during the third.

A notable feature of the jaundice thus occasioned is the behaviour of the bile acids. During the first stage, when the bile pigments are increased, the bile acids are diminished. Hence their appearance in the urine does not coincide with that of the bile pigments; for whereas the latter are present in quantity fifteen to twenty hours after the injection, the bile acids do not appear till about the twenty-second, thirty-first, or forty-eighth hour; in the next twenty-four hours they reach their maximum, diminish during the following twenty-four hours, and then disappear altogether.

Afanassiew supplemented these observations in one important particular by shewing, what Stadelmann at first failed to recognise, that the drug exercises a markedly destructive action on the blood—an observation which appeared to supply the missing clue to the explanation of the jaundice. According to Stadelmann the sequence of events is as follows: The drug causes a destruction of blood; the haemoglobin liberated leads to an increased formation and excretion of bile pigments (polychromia); this is attended by an increased viscosity of the bile, which, at the low pressure at which the bile is excreted, causes a temporary obstruction, with reabsorption of the bile and jaundice; and, finally, when the action of the drug exhausts itself, the bile gradually loses its viscid character, the flow of bile is re-established, and the jaundice disappears. A jaundice which thus had every appearance of being essentially haemato-genous, even in respect of the absence of bile acids from the urine in the first instance, at a time when bile pigments were present in quantity, was thus shewn to be really of obstructive origin, and to depend upon alterations (increased viscosity) in the bile. He found, moreover, that a similar explanation applies to other varieties of jaundice associated with increased destruction of blood.

Thus, *poisoning with arseniuretted hydrogen* occasions a remarkable concentration of the bile—the gall-bladder and bile-ducts being filled with a thick, viscid bile frequently containing large quantities of amorphous sediment, as well as numerous crystals of bilirubin. The increase of bile pigments in the bile absolutely amounts to as much as $3\frac{1}{2}$ times the previous amount; and relatively is still larger (20 times), as the quantity of bile is reduced $5\frac{1}{2}$ times. Yet, notwithstanding this striking increase in bile pigments, the bile acids are in no way increased, indeed they are reduced to one-tenth their normal amount—the same dis-

proportion between bile pigments and bile acids being thus shewn as in the case of toluylenediamine poisoning.

In the case of this agent Stadelmann conceives that "the destruction of the blood is the occasion of the jaundice—only, however, through the agency of the liver, which produces an abnormal bile in consequence of the abnormal blood conveyed to it."

Lastly, a similar explanation would appear to apply to the jaundice occasionally met with in conditions of haemoglobinaemia, whether induced by injection of free haemoglobin or of distilled water. Stadelmann's observations shew that changes in the bile are induced thereby, namely, increase of bile pigments, increased viscosity of bile and diminution of bile acids—changes similar in character, although by no means so marked in degree, as those produced by toluylenediamine or arseniuretted hydrogen.

The Obstructive Nature of Toxic Jaundice.—For the whole group of cases of jaundice accompanying increased destruction of blood, the foregoing observations shew conclusively that the jaundice is really obstructive in its nature, albeit the obstruction is temporary in character, and dependent upon an increased viscosity of the bile induced by the changes in the blood. It is really then hepatogenous, not haematogenous; but to signify its dependence upon the preceding blood changes it might be described, as Afanassiew has proposed, by the term *haemo-hepatogenous*.

The importance of this conclusion in relation to the pathology of so-called non-obstructive jaundice cannot well be over-estimated. For it will be obvious that the great majority of the conditions in which this variety of jaundice is assumed to occur—pyaemia, acute yellow atrophy, malaria, paroxysmal haemoglobinuria, and so forth—are precisely those in which increased blood-destruction is either obvious or likely to be present.

Nor does their significance end here. The observations throw light not only on the class of cases formerly described as haematogenous, but also on those obscure forms of jaundice regarded as due to suppression. The jaundice attending *phosphorus poisoning* was formerly adduced as an exemplary instance of a jaundice due to suppression of the hepatic function. Stadelmann's observations, however, shew that this form of jaundice depends upon bile changes similar in character to those above described, although much slower in production. Ten hours after administration of phosphorus the bile begins to be darker in colour; the bile pigments are increased by one-half; the bile acids are diminished. For the next twenty-four hours these conditions persist, and no jaundice is manifested. Then the bile begins to change its character; it becomes clearer, more mucoid, and much diminished in quantity (one-fifth); the bile pigments fall to one-half or one-third of their normal amount, and the bile acids are even more reduced (0·1, 0·15, or 0·7 instead of the normal 1·96). At this stage jaundice appears and slowly reaches its maximum about five days after the administration of the poison. The jaundice then slowly disappears, its disappearance being

marked by an increased excretion of bile pigments doubtless derived by reabsorption from the tissues. The bile acids still remain in defect for some days longer ; and it is not till the tenth or eleventh day that they once more regain their normal amount.

Cause of the Obstruction.—The foregoing observations shew that the obstruction is due to increased viscosity of bile. As this change appears to be an important factor in all cases of jaundice connected with blood disorder, it becomes a matter of importance to determine the precise cause of it. The matter has been worked out more especially in connexion with one drug—toluylenediamine. The jaundice produced by this drug has a peculiar interest, so intense is it, and so regular in its occurrence. In large doses it reproduces all the features of a severe jaundice, with fever, and swelling of spleen and liver, such as is met with clinically, for instance, in severe forms of *icterus gravis*, Weil's disease, or yellow fever. Three different opinions have been advanced to account for the obstruction in the bile-ducts occasioned by this and similar poisons.

(a) Afanassiew considers the chief factor to be the compression of the smaller bile capillaries from without. As the result of the action of the drug, he finds dilatation of the blood-vessels and lymphatics of the liver, and a blocking of the capillaries with altered red corpuscles. He believes that the drug exerts an irritant action on the liver, causing a hyperaemic and oedematous state of its tissues, and consequently a compression of the bile capillaries. Of this view it may be said that the jaundice is out of all proportion to the alleged mechanical cause, and that far greater dilatation of blood-vessels is met with—in congestion of the liver, and in other conditions, without the occurrence of any such obstruction.

(b) According to Stadelmann the chief factor is undoubtedly the increased viscosity of the bile, a change he conceives to be connected in some way with the increase of bile pigments (*polychromia*). In his view the jaundice might be most fittingly called "jaundice from polychromia." Besides this polychromia, he considers that there is probably another factor in some special action of the poison which leads to the secretion by the liver-cell of a more concentrated bile, too thick to flow away. He concedes to Afanassiew that possibly at the same time the liver-cells are affected, press upon the bile capillaries, and cause absorption of bile. He thus contemplates a number of possible factors; but he attaches the chief importance to one—the increase of bile pigments. It is clear, however, as I have shewn elsewhere (19), that this increase cannot be the chief factor ; if it were, the obstruction ought to be proportional to the increase of bile pigments. Stadelmann's own observations, indeed, shew that this is not so. Jaundice may be most intense with only a slight (one-half) increase of bile pigments (toluylenediamine) ; whilst, on the contrary, it may be slight or absent with a very great (three or fourfold) increase (arseniurated hydrogen poisoning).

(c) The conclusion I draw from my experiments in this matter is that the cause of the increased viscosity of the bile is an extensive catarrh of the intrahepatic bile-ducts from their origin downwards. In severe cases

this catarrh may extend into the duodenum itself, and there cause the most intense inflammatory swelling and congestion of the mucous membrane, beginning definitely at the orifice of the bile papilla ; the viscid catarrhal mucus which covers its surface being of the same character as that exuding from the bile-duct itself. A duodenal catarrh is, however, not necessary to this production. For the jaundice occurs even when the bile-duct is cut away from the duodenum (as in dogs with biliary fistula). This catarrh is excited by the excretion of bile containing the poison itself, or irritant products of it, along the bile-ducts. I found the poison in the bile increasing in quantity from the first hour onwards. The catarrh causes, to begin with, an increased viscosity of bile (1st stage) ; as it becomes more intense, catarrhal mucus fills the bile-ducts to the exclusion of bile pigments (2nd stage) ; and it then passes gradually off as the poison is eliminated (3rd stage).

The chief feature of this catarrh in ordinary cases appears to me to be not so much its high degree as its excretory origin ; beginning, as it does, in the smaller bile-ducts. Under the low pressure at which the bile is secreted, a very slight catarrh, set up by the excretion of an irritant through the liver, may from its widespread character easily set up obstruction enough to cause some reabsorption of bile and some degree of jaundice. The jaundice so occasioned is, I conclude, proportioned, not to the amount of the accompanying blood-destruction (haemoglobinaemia), nor to the increase of bile pigments (polychromia), but to the irritant character of the substance or substances excreted in the bile. *A poison (or its products) is likely to cause jaundice in proportion as it is capable of exciting catarrh of the bile passages during its elimination by the liver.*

Toxaemic as distinguished from Duodenal Catarrh of Bile-Ducts.—According to these observations, I recognise a "descending" as distinguished from a duodenal or ascending catarrh as a cause of jaundice. This variety of catarrh of the bile-ducts may, as I have suggested, be called toxæmic, to distinguish it from the ordinary duodenal origin of catarrh of bile-ducts which is assumed to arise and travel up the bile-duct from the duodenum. In this latter case the catarrh is supposed to create obstruction and to lead to jaundice by blocking the opening of the bile-duct with a plug of mucus. Only in this sense is it spoken of by Murchison ; this teaching as to the mode of origin of catarrhal jaundice has, however, been much questioned, and it has been suggested that the jaundice is really due to pressure exerted on the bile-duct by the head of the pancreas enlarged from catarrhal inflammation (Robson, 1904 ; S. Phillips, 1907). Stadelmann seems to have considered the duodenum to be the necessary starting-point of jaundice of catarrhal nature ; for in his experiments, when the bile-duct was ligatured off from the duodenum, and yet the jaundice still occurred, he regarded this result as conclusive of the "non-catarrhal" nature of the obstruction. The possibility of a catarrh spreading, not upwards from the duodenum, but down the bile-ducts from their origin, seems not to have

presented itself to his mind. And yet such a catarrh would obviously be of the first importance in the pathology of a jaundice connected with blood disorder set up by poisons. I consider, indeed, that in all probability this is a more common cause of catarrh of the bile-ducts, and consequently a more common cause of jaundice, than catarrh ascending from the duodenum. Both varieties of catarrh—the toxæmic and the duodenal—imply the action of an irritant, the one exerted on the bile-ducts in the course of its excretion with the bile from above downwards, the other on the duodenum and the mouth of the bile-duct. Of the two the former is the more likely, from its widespread character, to produce an obstruction sufficient to cause jaundice. It is certain, at least, for the reason already stated, that in the case of jaundice due to poisons a duodenal catarrh is not necessary for the production of the jaundice. If it occur, and it is only in the case of severe poisons that it does occur, it is not primary, but secondary to a previous catarrh set up in the bile-ducts during the elimination of the poison.

(II.) **The Relation between Jaundice and Blood-destruction.**—It has been seen that in nearly every case a notable feature of the blood disorder caused by these various icterogenetic poisons is an increased haemolysis variously manifested by morphological changes in the blood, by increased formation of bile pigments derived from haemoglobin, by presence of haemoglobin in the urine (*haemoglobinuria*), or by all these combined. The connexion between increased liberation of haemoglobin (*haemoglobinaemia*) and jaundice appears so close that, as we have seen, it formed in Kühne's hands the basis of the haematogenous doctrine. In his view an excess of free haemoglobin in the blood sufficed of itself to cause bile pigments to appear in the urine. The later experiments of Tarschanoff and Stadelmann appeared to establish the connexion more closely: the former always found bile pigment in the urine of dogs after injection of water or haemoglobin into the blood; the latter found that in such circumstances important changes occurred in the bile, such as increase of viscosity, leading to temporary retardation in its flow and consequent absorption of bile pigments into the blood.

As I have shewn elsewhere, the connexion between haemoglobinaemia and jaundice is neither so close nor so constant as at first sight appears. On the one hand, there is some reason to doubt the constancy or frequency with which bile pigment is to be found in the urine under such circumstances. The results on which Kühne's view is based have been obtained in one kind of animals only (dogs), and not invariably in them. Now, experiments on these animals are open to this great source of fallacy, that bile pigment is not infrequently present in the urine even of healthy dogs. And the experiments of Naunyn, as opposed to those of Tarschanoff, conclusively shew that even in dogs marked haemoglobinaemia—sufficient to cause *haemoglobinuria*—does not necessarily cause bile pigments to appear in the urine. Naunyn caused *haemoglobinuria* by injecting haemoglobin subcutaneously; yet in only 2 out of 6 cases did the urine react to Gmelin's test (bile pigment); and in both these cases the urine

had given the same degree of reaction before the experiment. In other kinds of animals, such as cats or rabbits, the most intense haemoglobinuria may be produced without any trace of jaundice (Steiner, Legg, Brunton, Hunter (19)). And the same rule applies to man. The most intense haemoglobinuria may occur without a trace of bile pigment in the urine, and without a trace of jaundice (for example, paroxysmal haemoglobinuria).

It appears to me, then, that the jaundice depends upon some factor other than the mere amount of haemoglobin set free. The relation between it and the blood-destruction is, in my opinion, no simple quantitative one as Kühne assumed. The jaundice may be absent even when the haemoglobinaemia (with haemoglobinuria) is intense; as in paroxysmal haemoglobinuria, or in blood-destruction by injection of distilled water. It may be extreme when there is no haemoglobinuria, as in *icterus gravis*, Weil's disease, or toluylenediamine poisoning in dogs.

Nor is the jaundice simply related to the increase of bile pigments due to the preceding blood-destruction—simply a “jaundice from polychromia,” as Stadelmann has suggested. For here again I would point out that the relation is not constant. Jaundice may be slight or absent when the increase of bile pigments is very great, as in poisoning with arseniuretted hydrogen, or in pernicious anaemia; or, on the other hand, it may be extreme when the increase is only relatively moderate, as in toluylenediamine poisoning. Thus, neither as regards amount of haemoglobin liberated, nor as regards bile pigments formed, is the relation a mere quantitative one. The relation is clearly rather of a qualitative than of a quantitative character. Different agents present certain differences in their mode of action on the blood, to which importance has been attached by certain observers in this relation (Afanassiew, Silbermann). Some, such as glycerin or distilled water, cause intense haemoglobinuria, leaving but a small proportion of haemoglobin to be dealt with by the liver and other organs. Others appear rather to break up the red corpuscles into fragments which accumulate in the liver (and other organs), a portion only escaping through the kidneys; and the increased excretion of bile thereby occasioned is liable to be attended with jaundice. To this class belongs the chief jaundice-producing agent—toluylene-diamine. A third group, like pyrogallic acid, are intermediate in their action, causing both haemoglobinuria and a slight degree of jaundice.

Whatever interest such differences may have, they are, I consider, insufficient of themselves to account for the great difference in the action of the above-mentioned agents in producing jaundice (19). Doubtless they may serve in some degree to explain why one kind of agent causes haemoglobinuria more than another; but they quite fail to account for the remarkable facts we have already observed—why, for instance, one drug which causes but a limited amount of blood-destruction, without haemoglobinuria, is capable of producing intense jaundice; while another which causes a much greater blood-destruction, and an intense haemoglobinuria, fails to produce any jaundice at all.

In addition to the haemolytic changes in the blood and increase of pigment in the bile just noted, the foregoing observations have revealed another change of more importance than any other in relation to this subject of jaundice. This change is increased viscosity of bile, amounting at the height of the jaundice even to a substitution of it by clear viscid mucus free from bile. To this more than to any other change I find the degree of jaundice related, and the degree of obstruction proportioned. I have shewn for the chief of these icterogenetic poisons that this viscosity is due to extensive and widespread catarrh of the bile-duct set up by the irritant action of the poison (or of its products) in course of its excretion in the bile—an irritant action so great that in certain cases it may excite the most intense duodenitis.

It is not its destructive action on the blood, but the action of the poison on the liver-cells and epithelium of the bile-ducts during its excretion, that appears then, so far as our observations go at present, to be the chief determining factor in the occurrence or non-occurrence of jaundice in disorder of the blood. The liability of a poison to produce jaundice is, I consider, proportioned to its irritant action on the epithelium of the bile-ducts in the course of its excretion through the bile, not to its power of causing blood-destruction. To this variety of catarrh the name *toxaemic* may be conveniently applied, to distinguish it from the ordinary form of catarrhal jaundice of duodenal origin, from which it is essentially distinct. The term *toxaemic* indicates the blood origin of the condition; that it is produced by excretion of poisons from the blood through the bile. It also indicates the chief character of the clinical features of these cases of jaundice which are mainly of a toxic character.

(III.) **Jaundice by Suppression ; "Ictère hémaphéique," "Urobilin icterus."**—In the class of cases hitherto considered it has been assumed that the jaundice has been always marked by the presence of bile pigment in the urine. There is a class of cases, however, to which reference must now be made in which this is not the case; in which, with a discolouration of skin hardly distinguishable from that of jaundice and a high colour of the urine resembling that of jaundiced urine, the pigments in the urine are not bile pigment, but other pigment derivatives of haemoglobin. The coloration of skin in these cases is usually not so deep as that found in ordinary obstructive jaundice; and it is of a more dirty earthy tint.

This kind of jaundice has received various names at different times. It constitutes one of the many forms of "jaundice by suppression" of older writers; it was named by Gubler (1857), and French writers following him, "l'ictère hémaphéique"; it is the "urobilin" or "acholuric" icterus of more recent writers. These names are by no means equivalent, but they are conveniently considered together, because the first three imply that the cause of the discolouration is the presence of pigments circulating in the blood as the result of some faulty excretion, or even of entire suppression of function of the hepatic cell.

Of all the various opinions regarding the mode of origin of jaundice,

that of a *jaundice by suppression* is both the oldest and the one most firmly rooted. We have seen that the class of cases referable to this category has been very greatly narrowed by recent observations. But even when all the cases arising in connexion with the action of poisons and with increased blood-destruction are excluded, as now they must be, there still remain the few cases that suffice to raise the questions : "What is to be understood by suppression of liver function ? Does it occur ? If it does, what part does it play in producing jaundice ?" In other words, is it possible for the liver-cell, without undergoing structural change, to cease to act altogether ?

I have said "without structural change" ; for this is the only point on which any difference of opinion can reasonably exist. It is obvious that a liver-cell structurally disorganised, as is the case in the later stages of many liver diseases—notably in acute yellow atrophy—must fail in its functional power. Moreover, there can be no doubt that many of the poisons capable of inducing jaundice affect the liver-cells injuriously, both in their structure—causing fatty parenchymatous degeneration—and in their function also. Indeed the latter may be said to have been shewn beyond doubt ; for it has been found, experimentally, that under the influence of poisons or other depressant factors, such as injury of the liver, haemoglobin may pass through the liver-cell unchanged, and be found free in the bile ; an occurrence which never takes place otherwise. These facts may be admitted. But the conception of suppression implies something more than mere functional disorder ; it implies that, as the result of certain influences—nervous as well as toxic—the liver-cell can dynamically be suddenly thrown out of action without any necessary static change, and that the effect of this arrest of function is to dam up within the blood the bile pigment which would otherwise have been duly excreted.

It is this doctrine which meets us at every point when we consider the pathology of jaundice, and which therefore must be considered in more detail. In a more or less modified form it is still held to apply to the jaundice of mental emotion, and indeed to some of the forms of jaundice produced by poisons ; but the data on which it is based are for the most part exceedingly indefinite. So long as the view was held that the bile pigments are formed in the blood, their mere retention in the blood and tissues and appearance in the urine, especially when unaccompanied by any bile acids, were deemed sufficient to point to suppression of liver function. But, as I have shewn, such a view is no longer tenable. Bile pigment is not formed within the blood, but within the liver-cell ; and its presence in the urine, even when unaccompanied by bile acids, is quite compatible with excessive activity of the liver-cells.

There remain three classes of facts which may be held to denote some interference with the functions of the liver in certain cases of jaundice : (a) Presence of pigments other than bile pigment in the urine in these cases ; (b) Changes in nitrogenous metabolism met with in the severest

forms of jaundice, for instance, diminished excretion of urea and the appearance of leucine and tyrosine in the urine ; (c) Presence of colourless mucus in the biliary passages, and absence of bile (Moxon).

(a) *Evidence of Suppression derived from a Study of Pigments other than Bile Pigment.*—In many severe cases of jaundice the urine presents a depth of colour far in excess of what can be accounted for by the quantity of bile pigment present, and obviously denoting the presence of abnormal pigments. Gubler was led by observation of this to distinguish two forms of jaundice : *l'ictère biliphéique*, due to the presence of bile pigment in the tissues ; and *l'ictère hémaphéique*, due to the presence of a hypothetical pigment, "hemaphein." He considered that if the liver were thrown out of action by poisons or other influences it could no longer transform haemoglobin into bile pigment ; the colouring matters in the blood would accumulate there, and undergo various modifications before their excretion in the urine.

Various organic diseases of the liver, such as cirrhosis and cancer, could bring about a similar suppression. Indeed cases of ordinary obstructive jaundice, if unduly prolonged or intense in degree, would lead to the same result.

This view of Gubler has now only a historical interest, inasmuch as the pigment he termed *hemaphein* never had more than a hypothetical existence. So far as it conforms in its characters to any definite urinary pigment, it approximates most closely, as Quincke has shewn, to urobilin. And since Gubler's time, the class of case to which his view referred has been most frequently discussed under the title of urobilin jaundice.

Urobilin Jaundice.—First recognised as a normal pigment of the urine by Jaffé in 1863, urobilin was soon afterwards (1871) shewn by Maly to be identical with one obtainable by reduction from bilirubin, the chief bile pigment ; and, subsequently (1874), Hoppe-Seyler succeeded in preparing it artificially from haematin. Since the important observation made by Müller (1892) that intestinal micro-organisms possess the power of transforming bilirubin into urobilin, evidence has steadily accumulated that this is probably the ordinary mode of origin of urobilin (enterogenous origin). But the possibility of other modes of origin of urobilin in certain special circumstances cannot be altogether excluded. Thus, it might be produced either from haemoglobin (a) in the liver (hepatogenous origin) ; (b) in the blood (haematogenous origin) ; (c) in the tissues (histogenetic origin) ; or from bilirubin (a) in the tissues (histogenetic origin) ; (b) in the kidney (nephrogenous origin). Urobilin is a normal constituent of the urine, and especially abundant in febrile urines ; but the conditions under which it is met with in excess are those in which large extravasations of blood are being absorbed (haematoceles), or an abnormal destruction of blood is occurring (pernicious anaemia) ; conditions I have elsewhere shortly defined as "an excessive destruction of haemoglobin unattended by haemoglobinuria."

Its presence under such circumstances has a special interest in relation to our present subject, as it is not infrequently associated with a

certain yellowish, apparently icteric tinge of skin and conjunctiva. It is this association that has led some observers to apply to the condition the title *urobilin jaundice*.

The precise conditions which determine the amount of urobilin in the urine in cases of jaundice are as yet but ill defined. In jaundice of a severe type, due to total occlusion of the common duct, the urine contains bilirubin, but no urobilin; the faeces likewise contain little or no urobilin. When the obstruction is removed, the bilirubin in the urine diminishes, and the urobilin rapidly rises.

The group of cases of severe jaundice in which there is abundance of bile pigment in the urine, and only a trace of urobilin, cannot be accounted for on any view which implies that urobilin is formed from bilirubin within the tissues. But in the light of the more recent observations referred to, establishing the intestinal origin of urobilin from bilirubin by the action of micro-organisms, this class of cases becomes clear. For in severe jaundice, with no bile entering the intestine, the formation of urobilin ceases. Conversely the conditions in which urobilin might be expected in excess are those in which, along with some degree of jaundice, there is also an increased secretion of bile pigments; and it is precisely in such conditions—those of *haemo-hepatogenous jaundice* already considered—that urobilin is usually found in excess.

In cases of urobilinuria with an icteric tint of the skin and conjunctivae, examination of the blood-serum shews that it contains bile pigment, and that there is a true jaundice (Theile). The amount of bile pigment in the blood is small, and not sufficient to appear in the urine. This condition has been called acholuric jaundice (Gilbert and Herscher), and is closely allied to the condition called simple family cholaemia (Gilbert and Lereboullet). The so-called urobilin jaundice is therefore a true jaundice, but is associated with urobilinuria, due to the formation of urobilin from bilirubin in the intestines.

For the group of cases of so-called suppression jaundice, in which the suppression is ascribed to nervous influences, I find no evidence whatever that the pigments excreted differ in any way from those of ordinary obstructive jaundice; or that there is any "suppression" of excretory function on the part of the liver (see p. 72).

In severe toxæmic conditions—such as characterise the gravest forms of jaundice, malignant jaundice, acute yellow atrophy, and the like—where the liver is extensively disorganised, and the excretion through the kidneys is interfered with owing to degenerative changes in the cells of the tubules, it is probable that abnormal pigments may be formed, and may give a special character to the coexistent jaundice. We know that in septic conditions of the blood—and in all severe cases of jaundice haemorrhages are almost a constant feature—the haemoglobin is more unstable than in health. Thus, as Dr. Copeman has shewn, if a drop of putrid serum be added to healthy blood under a cover-glass, crystals of reduced haemoglobin appear in from twenty-four to forty-eight hours; whereas normal blood alone undergoes no crystallisation. On the other hand, in

certain toxic conditions—for example, cancrum oris, septicaemia, erysipelas, pernicious anaemia—the blood readily crystallises without addition of any putrid serum. Chauffard (1908) has also emphasised the fragility of the red blood corpuscles in toxæmic jaundice. It is very probable that, in severe forms of blood disorder marked by jaundice, abnormal pigment derivatives of haemoglobin may be formed and be excreted in the urine. But their presence in such circumstances does not necessarily indicate a suppression of the excretory function of the liver, as the suppression conception of jaundice implies. It is sufficiently accounted for by disordered function of the liver consequent on the toxic condition of the blood. But functional disorder is a condition wholly distinct from total suppression of excretory function.

Thus a liver-cell, under the influence of a severe poison, may have its functions so affected that, instead of breaking up haemoglobin into normal bile pigment, it produces abnormal bile pigments; and this of itself is sufficient to account for the presence of abnormal pigments. But that under the influence of mental emotion, or the action of a severe poison, the whole of the liver, without undergoing previous structural change, may cease to work, and that the effect of such a suppression is to produce jaundice, damming up bile pigment or allied pigments, finds, in my opinion, no support whatever from any facts concerning the character of the pigment, urinary or other, excreted in such cases.

(b) *Evidence of Suppression derived from a Study of Changes in Metabolism.*—The second class of facts adduced as evidence of suppression of liver function in jaundice is the occurrence of marked changes in the nitrogenous metabolism in severe cases of jaundice—for example, diminished excretion of urea; appearance of leucine and tyrosine in the urine.

Thus with regard to the jaundice produced by phosphorus—once cited as an eminent example of a jaundice from suppression—in the first observations made (Schultzen and Riess, 1870), the urea appeared to be reduced almost to vanishing-point. Münzer (1894) subsequently estimated the total excretion of nitrogen in 10 cases of phosphorus poisoning, determining at the same time the proportions of urea, uric acid, ammonia, and extractives of which the total was made up (*vide p. 133*). His observations shewed that, so far from the excretion of urea being diminished, after the first twenty-four hours when the vomiting has ceased, the excretion continues up almost to a few hours of death, in quantities approaching those of health; and far exceeding what would be formed by a healthy liver in the absence of food. Since all recent observations agree in pointing to the liver as the chief seat of urea-formation, this excretion is such as to denote that a very active metabolism is going on within the liver up to within a few hours of death. This conclusion is brought out still more clearly by some further facts. As an indication of the degree of liver activity, even more important than the actual amount of urea formed, is the proportion of urea to the total nitrogenous excretion. The experiments of Schroeder have established satisfactorily that the liver is the chief seat of the formation of

urea, and that it is formed there by a process of synthesis from ammonia. In health *urea* constitutes about 85 to 90 per cent of the total nitrogenous excretion, *ammonia* from 4 to 6 per cent; the remainder being in the form of *extractives*. If the liver be cut off from the circulation there is a marked fall in the proportion as well as in the amount of urea, and a corresponding rise in the proportion of ammonia. Now, in phosphorus poisoning the proportion of urea is but little reduced (80 instead of 90 per cent), the corresponding increase of ammonia being moderate (10 to 18 per cent instead of the normal 4 to 6 per cent). This alteration, slight though it be, might be held to indicate that the functional activity of the liver is affected—is “suppressed” to that extent; but even this significance cannot be attached to it. Apart altogether from activity of the liver, there is one condition which more than any other influences the amount of ammonia excreted, namely, the degree of alkalinity of the blood. Anything that lowers the alkalinity of the blood below the normal standard raises the proportion of ammonia excreted in the urine at the expense of the urea. Now acidosis exists in phosphorus poisoning, and Münzer has shewn that the increased ammonia excretion depends on acidosis and not on any impaired activity of the liver; he administered sodium bicarbonate to a patient with acute phosphorus poisoning, and found that the excretion of ammonia rapidly diminished (*vide p. 133*).

To sum up, then, with regard to the jaundice of phosphorus poisoning, the facts shew that at the time at which the jaundice makes its appearance the liver functions are by no means suppressed. For not only is there an increased formation and excretion of bile pigments (Stadelmann), but, notwithstanding the absence of food, urea also continues to be formed in large quantity up to the last few hours of life, in amounts approximating those of health (Münzer).

(c) *Absence of Bile from Bile Passages as an Evidence of Suppression.*—The fact that in certain cases of jaundice the bile passages are found filled with an almost colourless mucus, instead of bile, has been much insisted on by Moxon and others as an evidence of suppression of excretory function on the part of the liver. But as pointed out, in my opinion correctly, by Dr. Wickham Legg, the presence of such mucus in the large bile-ducts is only evidence that the obstruction is higher up—in the smaller ducts. “These continue to receive the bile poured into them by the lower cells, but the bile does not reach the large ducts because the smaller are shut off from the large either by plugs of tenacious mucus or by gravel.” Although the larger ducts are colourless, the smaller ducts can be found stained with bile. Stadelmann’s experiments shew that in the jaundice produced by poisons the bile becomes viscid and mucoid at the time the jaundice is most intense. Examination of the liver itself at this time shews the smaller bile-ducts and capillaries to be filled with thick, viscid, highly pigmented bile.

Conclusion.—Neither the facts concerning the pigments nor those concerning nitrogenous metabolism appear to lend any support to the

hypothesis of jaundice by suppression without structural change. There is no conclusive evidence that a healthy liver can be suddenly thrown out of action, whether by nervous action or the action of a poison ; or that jaundice can thus be caused. There is evidence on the contrary that a liver so obviously diseased as the liver in phosphorus poisoning is, continues to discharge some of its most important functions almost unimpaired within a few hours of death.

Nor is my judgment as to this hypothesis affected by the modification of it put forward by Liebermeister (1893). He considered that in certain cases, under the influence of mental emotion or action of poisons, there may be suppression of only one particular function of the liver-cell. Apart from forming the bile pigments, he considers one of the chief functions of the liver-cell to be that, notwithstanding its close relation to blood capillaries and lymphatics, it excretes its bile into the bile capillaries, and prevents it from entering the blood. For the discharge of this function the integrity of the cell is necessary. It is not to be assumed that cells profoundly affected by nerve influence or poison, as the case may be, will discharge this function properly. It is rather to be supposed that under such circumstances they will no longer be able to prevent direct diffusion of their contents into the blood and lymph, just as in renal disease the living endothelium of the vessels can no longer retain albumin. Apart, therefore, from any obstruction, jaundice, he says, might thus arise ; and all the more readily inasmuch as it is precisely in such cases that degenerative changes are found in the whole or in a large number of the liver-cells. He goes even farther, and conceives that the cell might be only partially affected in its functions, still being able to produce bile although no longer able to prevent its diffusion into the blood ; or that the cells in one portion of the liver might continue to produce bile, which afterwards comes into relation with others that have lost their power of retention. Jaundice so caused, by failure on the part of the liver-cell to retain its bile, he proposes to designate "akathctic" jaundice (*kathektikos* = retentive). This view is one capable neither of proof nor disproof ; one which, under any circumstances, could only be entertained when all other explanations fail.

(IV.) **Increased Secretion, with Excessive Absorption of Bile from the Intestine, as a Cause of Jaundice ; "Jaundice from Polychoilia."**—The cases so described correspond for the most part with those designated haematogenous. Of the latter, indeed, a polychoilia was deemed to be a distinguishing feature ; if the stools were free from bile, the jaundice was of obstructive origin ; if they contained bile, its origin was haematogenous.

We now know, in the light of Stadelmann's observations, that the jaundice in these latter cases is no less obstructive than in the former ; and that the cause of it is not the increase of bile (polychoilia) itself, but the increased viscosity of bile which usually accompanies the polychoilia. Indeed, exception is taken by Stadelmann to the use of the term "polychoilia" at all in this relation ; inasmuch as both its watery

constituents and its bile acids are usually diminished. It is really a "polychromia," an increase of bile pigments.

Even when this large group of cases is excluded, as now they must be, from the category of jaundice from polychoilia, we have still to inquire whether, as Frerichs taught, jaundice can result from increased absorption of bile from the intestine.

This teaching received the support of Murchison. He considered it to be the explanation of jaundice in congestion of the liver; in many cases of which, as he pointed out, the quantity of bile is increased. "The vessels of the liver are distended, and the diffusing surface of the walls is consequently increased, and more than the normal quantity of bile is taken up into the blood. . . . There is no obstruction of the bile-ducts unless there be concurrent inflammation of the duodenum and ducts; and sometimes indeed there is biliary diarrhoea. If the bowels be constipated, the jaundice from congestion of the liver will probably be increased, as the bile instead of being cleared away will accumulate in the biliary passage, and will be absorbed in all the larger quantity by the distended vessels. A sluggish state of the bowels often contributes to the development of jaundice, partly by impeding the portal circulation and inducing congestion of the liver, partly by causing an accumulation of bile in the biliary passages and duodenum, and thus favouring its absorption into the blood."

It is clear from the foregoing that although Murchison had chiefly in view an increased absorption from the bile passages, not directly from the intestine, he had also in view in such cases a direct absorption of bile into the blood-vessels of the liver from increase of their diffusing surface. In the light of more recent observations, it must, I think, be regarded as exceedingly doubtful whether such a direct absorption ever takes place. Saunders first shewed (1815) that, after ligature of the bile-duct, the chief absorption of bile takes place through the lymphatics. This has since been amply confirmed by several observers (Fleischl (1874), V. Harley (1892), Szubinski (1899)).

When it is remembered how close are the relations of bile capillaries and blood capillaries, separated as they are only by the thickness of the liver-cell interposed, the above results are very striking. That under these favourable circumstances bile is not reabsorbed by the liver-cells and does not enter the blood directly, but continues to be excreted into the bile capillaries and thence absorbed by the lymphatics, affords convincing proof that absorption of bile is not a matter of extent of diffusing surface between bile and blood capillaries respectively. Bile once excreted is absorbed only by lymphatics, not by the blood-vessels directly.

As regards congestion of the liver in particular, it is, I think, unnecessary to call in the aid of any unusual factor to explain its jaundice. That is sufficiently accounted for by the prevailing condition of congestion and catarrh, which favours temporary stagnation of bile in the bile passages with or without increased secretion of bile.

The view of a jaundice from polycholia implies, however, more than a mere absorption of bile within the liver, whether through lymphatics or blood-vessels. It implies that such an absorption may take place from the intestine ; that the absorption which normally takes place may become so increased that the liver is no longer able to dispose of all the bile pigment conveyed to it, and that some of it escapes into the general circulation and produces jaundice. This view assumes, first, that bile is normally absorbed from the intestine into the portal blood ; secondly, that this absorption may be so great that the liver cannot excrete all the pigment conveyed to it ; that is, there is a relative incompetence of the liver.

The basis for this view is the hypothesis of "the circulation of the bile" put forward by Schiff (1868). He observed that in dogs with biliary fistula the secretion of bile diminished when the bile was withheld from the intestine ; whereas it immediately became increased if the bile were allowed to flow again into the intestine. The same thing was observed if, instead of bile, bile salts were injected into the duodenum. He concluded that the increase arose from absorption of bile into the portal blood again to be excreted by the liver ; that what might be termed a "circulation of bile" thus took place within the portal system.

Similar observations were made by Rutherford and Vignal in their experiments (1876) : injection of bile into the intestine was followed by increased flow of bile. Together they afford at least presumptive evidence that a portion of the increase is actually due to the absorption and excretion of the injected bile. But although later observations conclusively shew (Tarschanoff, Wertheimer) that bile pigment injected into the blood is without doubt excreted in part in the bile, the evidence that increased absorption of bile from the intestine plays any part in producing jaundice remains still little more than presumptive.

That the liver exercises an important excretory and destructive function in respect of certain substances normally absorbed from the intestine in the portal blood is beyond dispute. And it may be regarded as equally beyond dispute that whatever bile pigment is absorbed in the portal blood is again excreted in the bile.

But what, in my opinion, is much open to question is the extent to which such an absorption occurs in health, and whether it is ever a factor in producing jaundice. Wertheimer's observations, striking as they are, I cannot regard as conclusive on the point. The bile of the sheep contains a pigment, with definite spectroscopic bands, not present in the bile of the dog. After injection of sheep's bile into the circulation of the dog Wertheimer was able to discover the pigment in the dog's bile.

Were jaundice produced in this way it would appear not only in the one condition adduced by Murchison of congestion of the liver, but in other conditions also where the increase of bile is even more marked ; namely, under the action of haemolytic poisons generally. But in all these cases, where a polycholia exists, the conditions favouring an absorption of bile into the circulation are created before the bile reaches

the intestine, namely, within the liver itself and its bile-ducts, and have been brought about by increased viscosity of bile. The jaundice is thus not of intestinal but of hepatogenous origin.

(V.) **The Influence of the Nervous System in Producing Jaundice.**

—The nervous system has long been credited with a very direct influence in the production of certain forms of jaundice.

According to some authors, indeed, disturbance of the nervous system plays a part of considerable importance in nearly all forms of jaundice, from the simplest "biliary attack" to the gravest form of all, namely, acute yellow atrophy of liver. The former malady has been regarded as an evidence of altered nerve function (Habershon); and in the latter, deranged innervation has been considered to play a chief part (Liebermeister), either by causing perverted secretion in which the liver-cells become broken up (Rokitansky), or by causing paralysis of the bile-ducts (von Dusch). In a considerable proportion of cases (one-tenth, Thierfelder) the only cause assignable for the disease has been the influence of fright, or some depressing mental emotion.

Apart, however, from these cases, the cases regarded as manifesting this influence more clearly are those in which jaundice has followed sudden or severe mental emotion or strain—such as fear, anger, or anxiety—either immediately or very soon after. Of this character, also, is supposed to be the jaundice following on concussion of the brain. The cases may be divided into two classes:—

(i.) In the one—an extremely small class—the jaundice is described as following immediately, that is, in a far shorter time than ordinary obstruction could produce it. Of this nature are the two cases of Villeneuve (1818) quoted by Murchison. A soldier, insulted in public, in a fit of furious anger became suddenly jaundiced, soon afterwards delirious, and died in convulsions. A priest had a sudden fright from the rush of a mad dog; he uttered a loud cry, fell down unconscious, and was taken up yellow as saffron.

(ii.) The other class of case—comparatively common—is where the jaundice occurs in the course of a few hours after anxiety or great mental strain. Of this nature is the case of the youth quoted by Sir Thomas Watson, who had an attack of intense jaundice apparently traceable to nothing but overdue anxiety about an approaching examination; or that of the doctor, who, while attending a case of puerperal haemorrhage, became deeply jaundiced in one night.

The mechanism of the jaundice in such cases is by no means clear. The features that appear to suggest nervous derangement as distinguished from obstruction, especially in cases of the first class, are, first, the suddenness of onset of the jaundice—the skin becoming yellow almost in an instant, whereas the jaundice from mechanical obstruction takes twelve to twenty-four hours or more to develop; and, secondly, the frequency with which such cases are said to be marked by cerebral symptoms—delirium, coma, convulsions.

(i.) Cases of instantaneous jaundice are admitted to be of great

rarity. Most of them date from the earlier history of the subject. But assuming such cases to occur, they raise points of interest as to the possible part taken by the nervous system in producing jaundice.

Various views have been put forward :—

(a) Like every other variety of obscure jaundice, it has been referred to *suppression* of liver function. Under the influence of powerful emotion the function of the liver-cell becomes temporarily arrested, and jaundice results. We have seen, however, that there is no theory of jaundice so unsatisfactory as this of suppression. If the jaundice in these cases were shewn to be produced by pigments other than bile pigments, there might be ground for assuming such a suppression ; but this is not so. The jaundice is due to the presence of bile pigments, formed as we have seen by the liver-cell ; and the problem is to account for their passage into the blood : whether they pass into the blood capillaries directly or indirectly in the usual way through the lymphatics.

The suddenness of onset would appear to point to direct absorption ; and it has been suggested (Brunton) that this might be brought about by some sudden fall of blood-pressure within the portal system, such as emotion might cause, followed by a sudden absorption of bile from the bile capillaries.

(b) This view raises the question of the *relation of the blood-pressure to bile secretion* in normal circumstances. The conditions within the liver are in this respect peculiar ; the liver obtains the chief material for its metabolism, including the formation of bile, from the venous blood-supply (the portal)—not from the arterial. The chief function of the hepatic artery is to supply the tissue framework of the liver. The main supply is through the portal system. It follows from this arrangement that, to an extent quite unusual in the case of any other organ, the supply of blood to the liver and its functional activity are independent of any direct vasomotor control. It is regulated rather in an indirect manner by the amount of blood entering the portal system through the intestine. Variations in the general blood pressure affect it little. Thus, Heidenhain found that a fall in the general pressure, even so great as one-half, appeared to influence the secretion of bile but little. On the other hand, variations in the portal pressure do affect it materially. Thus, stimulation of the spinal cord, or of the sensory nerves, by causing contraction of the splanchnic vessels and thus diminishing the amount of blood entering the portal system, occasions a diminished secretion of bile. And, conversely, section of the splanchnic nerves, by causing a dilatation of blood-vessels in the portal area, and thus increasing the flow of blood through them, occasions an increased secretion of bile.

The secretion and flow of bile being thus chiefly influenced by the flow of blood within the portal system, the question arises whether sudden and extreme variations in the direction of a fall of pressure can affect the flow of bile to such an extent as to arrest it altogether, and cause its direct absorption into the blood. Now even in health the pressure within the portal system is very low and, what is still more important, is

much lower (nearly two and a half times) than that at which the bile is secreted. The conditions might thus appear to be permanently favourable to a direct absorption of bile into the blood-vessels. And yet, as we have seen, so far is this from taking place that even after ligature of the bile-duct the bile cannot be made to pass into the blood-vessels. It is absorbed through the lymphatics. Whether, under the influence of emotion or other powerful nervous shock, these conditions can be altered, appears to me to be exceedingly doubtful.

(c) To account for the sudden onset of the jaundice in such cases another possible factor may be suggested as the result of sudden emotion, namely, *spasm of the bile-ducts*, at a time when the secretion and flow of bile are in active progress. Peristalsis of the walls of the bile-ducts and gall-bladder must play a prominent part in the propulsion of bile into the duodenum.

The effect of sudden emotion on the peristaltic movements of the intestine is well known. And it is conceivable that in rare cases—and, after all, the cases now under consideration are of extreme rarity—under the favouring conditions above described, sudden mental emotion of the nature of fear and anger might occasion a spasm of the bile-ducts of the nature here contemplated. Assuming that such cases occur, it is in this direction, rather than in that of suppression, or direct absorption into the blood-stream, that, as it appears to me, the most likely explanation of the jaundice is to be found.

(ii.) The more common class of cases referred to nervous derangement—those, namely, where the jaundice appears more gradually, albeit still quickly—say in the course of twelve or twenty-four hours or more—presents less difficulty, and can be accounted for without calling in the aid of such special factors. The effect of grief and anxiety in arresting digestion, and in producing acute indigestion with all the symptoms of gastric and duodenal catarrh, need not be dwelt on. In these cases the jaundice is doubtless of catarrhal origin—more sudden in onset than usual, it is true, but pursuing subsequently the same course and disappearing in about eight days.

SUMMARY OF THE VARIOUS FACTORS.—As possible factors, other than mechanical obstruction, in the causation of jaundice we have had to consider :—

1. Haematogenous origin of bile pigment ("Haematogenous Jaundice"). We have seen that the normal seat of formation of bile pigment is within the liver-cell. A haematogenous origin of bile pigment sufficient in degree to cause jaundice does not occur.

2. Suppression of function ("Jaundice by Suppression").

(a) Suppression of Biliary Function. Pigments other than bile pigment as a cause of jaundice ("L'ictère hémaphéique," "Urobilin Jaundice").

There is no conclusive evidence of any such causation of jaundice. Pigments other than bile pigment may be formed, and may in certain

cases produce some discolouration; but this is totally distinct from jaundice.

In many cases of jaundice evidence of altered activity of liver-cells is forthcoming; for example, diminished secretion of bile, increased formation of bile pigments, diminished formation of bile acids; but such changes cannot be regarded as indicating "suppression" of biliary function. On the contrary, in the larger number of such cases the most marked feature is an increased formation of bile pigments—evidence, therefore, of increased activity rather than of suppression of function.

(b) Suppression of Metabolic Function. Diminished formation of urea with appearance of leucine and tyrosine in the urine.

Besides the formation of bile, the formation of urea may be taken as an index of liver activity; all evidence going to shew that urea is formed by process of synthesis from ammonia, and that the synthesis takes place within the liver-cell.

In health urea constitutes about 85-90 per cent of the total nitrogenous excretion of the urine, the remainder being made up of ammonia and extractives.

In jaundice, even in the severest cases such as phosphorus poisoning, this proportion may remain unchanged, or at most slightly lowered; so that at the time the jaundice appears, no evidence is forthcoming of any "suppression" of liver function, as regards urea-formation, in the sense assumed by the "suppression theory" of jaundice; namely, suppression of function apart from structural alteration.

It is thus extremely doubtful whether total "suppression" of function ever occurs apart from actual destruction of the liver-cell. Hence it is only in the last stages of the severest forms of toxic jaundice—such as acute yellow atrophy of the liver—that the functions of the liver can rightly be said to be "suppressed."

3. Increased secretion of bile with excessive absorption from the intestine ("Jaundice of Polycholia").

Many cases of jaundice, those produced by poisons generally, are marked at one stage or other by increased flow of bile and increased excretion of bile pigment. There is no conclusive evidence that jaundice may result from increased absorption of this bile from the intestine. The jaundice met with under such circumstances is the result of absorption of bile from the bile-ducts.

4. Deranged innervation ("Jaundice of Emotion").

Deranged innervation plays a doubtful, and in any case quite a subordinate part in the production of jaundice.

(a) There is no evidence that jaundice can be produced by extreme fall of pressure within the portal system and absorption of bile direct into the blood.

(b) Sudden mental emotion may conceivably cause spasm and reversed peristalsis of the bile-duct, as of involuntary muscle generally.

The two important factors in producing jaundice are:—

5. Increased destruction of blood with increased supply of haemoglobin to the liver.

6. Action of poisons ("Haemo-hepatogenous Jaundice").

Both factors are conveniently considered together, as they usually operate together. Although operating together these two factors are not of equal importance. *The degree of jaundice is dependent more upon the nature of the poison than the amount of blood-destruction.* The most intense jaundice may be produced by poisons that cause but little or at most a moderate destruction of blood; for example, phosphorus and toluylene-diamine. Most of the severe forms of jaundice met with in disease—"Icterus gravis," "Malignant jaundice," "Weil's disease"—are of this character, and illustrate this point. On the other hand, intense destruction of blood may be attended with little or no jaundice. In both cases the jaundice is the result of absorption. It is caused by changes in the liver and in the bile, and is thus in every sense *hepatogenous*. Of most importance are the changes in the bile and smaller bile-ducts. The chief of these are—(a) increased formation of bile pigments (polychromia); (b) diminished formation of bile acids; (c) diminished quantity and increased viscosity of the bile itself. The viscosity retards temporarily the flow of bile along the bile passages; for a time it may arrest it altogether, and is the proximate cause of the absorption. In the case of the most notable jaundice-producing poison—toluylene-diamine—this increase of viscosity I have shewn to be due to a catarrh of bile-ducts, extending from above downwards (descending catarrh), produced by the excretion of the poison through the bile.

Instead, then, of the two varieties of jaundice formerly described, one *hepatogenous* or *obstructive*, the other *haematogenous* or *non-obstructive*, it is necessary now to recognise one class only. All jaundice is *obstructive*, the result of absorption of bile formed and excreted by the liver. The cause of the absorption may be obvious—mechanical obstruction (*Simple hepatogenous jaundice*), or more obscure and less easily demonstrable—swelling and catarrh of the lining epithelium of the bile passages, with consequent increased viscosity of the bile (*Toxaemic obstructive jaundice*).

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JAUNDICE IN NEWLY-BORN CHILDREN

By JOHN THOMSON, M.D., F.R.C.P.Ed.

THE most important forms of jaundice in very young infants, met with in this country, are icterus neonatorum, and those due to certain infective conditions of the liver and to congenital obliteration of the bile-ducts. Catarrhal jaundice, similar to that which occurs in adults and older children, is also occasionally seen soon after birth, but as the symptoms and pathology of these cases are the same as in later life, they need not be specially considered here. It may, however, be mentioned that new-born infants are apt to be very ill with catarrhal jaundice, although they generally recover. Jaundice is very rare in infants with congenital syphilis, although the liver is so often affected in them; for the intercellular cirrhosis which is the usual change present does not seem, by itself, to cause it. It does, however, occasionally occur to a very profound degree in syphilitic cases, as the result of pericholangitis, or from obstructive disease of the bile-ducts (*Rolleston, v. infra*).

Non-syphilitic "biliary cirrhosis" of the liver is extremely rare in

early infancy, in temperate climates, apart from obstruction of the bile-ducts. In India, however, an epidemic variety of this disease is well known, and is a serious cause of mortality in Bengal (Manson).

Buhl's disease (fatty degeneration of new-born children), which is a severe form of infective jaundice, and Winckel's disease (epidemic haemoglobinuria) are other rare and serious conditions in young babies, in which jaundice is a prominent feature.

ICTERUS NEONATORUM.—SYNOMYMS: *Normal, physiological, or idiopathic jaundice of new-born children.*

Description.—Icterus neonatorum is a mild form of transitory jaundice of uncertain etiology, which appears soon after birth in a large proportion of children otherwise normal, and passes off without subsequent ill effects.

Morbid Anatomy.—Nearly all the internal organs in these children shew a yellow tinge, and this is true even of such tissues as the cartilages, brain, and spinal cord, which in adult jaundice are not generally discoloured. The tinge, however, is but slightly marked in the spleen and kidneys, and in the liver it is rarely discernible to the naked eye even in the most severe cases. The intima of the arteries, the endocardium, and other serous membranes, and also the serous fluids, are deeply stained. The pericardial fluid contains not only bile pigment but bile acids also, as Birch-Hirschfeld, Hofmeister, and Halberstam have demonstrated.

The bile-ducts are normally formed and pervious; and apart from the general bile-staining of the tissues, no abnormality of any of the organs is discovered.

Pathology.—Numerous hypotheses have from time to time been propounded to account for icterus neonatorum. Many of these, such as those suggested by Virchow, Cruse, Epstein, Kehrer, Weber, Frerichs, Birch-Hirschfeld, and Quincke, have not been fully verified by subsequent observers and need not be discussed here. Although the exact way in which the jaundice comes about is still very obscure, it seems almost certain that it is hepatogenous in origin. The presence of bile acids as well as of bile pigment in the pericardial fluid of icteric new-born children, and their absence in that of others, proves conclusively that the yellow colouring-matter is really bile and comes from the liver. This effectually disposes of the view that the condition is a purely haematogenous form of jaundice, and also of the old notion that it is not jaundice at all, but merely a kind of local discoloration due to the red of the hyperaemic skin turning yellow, as a bruise does in the process of fading. It also seems certain that the jaundice depends on some slight alteration in the normal physiological changes which occur in the infant's vital processes during the first few days of life. Soon after birth very great changes take place, not only in the child's respiratory, digestive, and circulatory systems, but also in the composition of the blood. At birth there is a great excess of red blood-corpuscles, and they are very rich in haemoglobin. During the first week of life a large proportion of these undergo destruction (Hofmeier, Silbermann); the excretion of these

haemolytic products by the liver renders the bile concentrated and viscid, and thereby leads to its stagnation and consequent reabsorption. Porak considers that delayed ligature of the umbilical cord is one of the chief causes of icterus neonatorum ; and this has been shewn by Bauzon to cause a great increase in the quantity of the infant's red blood-corpuscles. According to Abramov, the backward pressure in the biliary capillaries prevents the liver-cells from disposing, in the normal manner, of the bile that they form, which therefore passes into the blood-vessels.

Clinical Features.—The disorder is an extremely common one, being met with, in a more or less marked degree, in a very large number of new-born children. Thus, Runge states the proportion of infants affected in this way as 80 per cent, Porak as 79-90 per cent, and Bouchut as 80-90 per cent. Probably the lowest proportion given is that of Holt, who reports that of 900 children born in the Sloane Maternity Hospital in New York 300 were icteric.

It seems to be a matter of general experience that this discolouration is more frequently observed in hospital than in private practice. This has been attributed to the weakness of hospital infants ; but this may be but an apparent prevalence due to the good light more uniformly obtainable in institutions than in the bedrooms of private houses. Certainly, however, it is more common in weakly infants with atelectasis, and in those that are born prematurely. The presentation at birth, the duration of the labour and its character—whether natural or artificial—are said to have no influence upon its production (Holt) ; and it is doubtful whether one sex is more affected than the other.

The yellowness of the surface of the body is generally the only discoverable symptom, the children in all other respects being perfectly well. The icteric tint is usually seen for the first time on the second or third day of life, or a day or two later. It increases in depth for one or two days and then slowly disappears. In slight cases it may be quite gone in three or four days ; often it lasts a week or more ; but rarely, and in very severe cases only, does it persist for more than a fortnight. The degree of the discolouration varies from the slightest perceptible tinge to a deep yellow. When extremely slight it is best detected by pressing the point of the finger on the infant's red skin, and looking for a yellow tinge on the pale spot which the pressure produces.

The distribution of the jaundice and the order of its appearance are somewhat peculiar. First, and most distinctly, it is seen on the skin of the face—especially on the forehead and round about the mouth—and on the chest ; later it appears in the sclerotics, and last of all on the hands and feet. Compared with the skin, the sclerotics are usually but slightly affected, and sometimes they remain quite normal in appearance. The slight and late implication of the eyes in these cases is an interesting point, as in ordinary obstructive jaundice the sclerotics are usually among the parts first and most deeply affected. The peculiarity is perhaps better expressed by saying that the skin in this form of jaundice is particularly early and particularly deeply tinged. This makes the

degree of the jaundice appear much greater than it really is; this is to be attributed to the hyperaemia of the new-born infant's skin (Cruse).

The urine, in most cases, appears quite normal, and does not leave a yellow stain on the child's napkins. In severe cases, however, bile pigment is present in it to such an extent as to discolour it. Parrot and Robin found small, amorphous, irregular masses of yellow pigment, sometimes floating free in the urine, sometimes embedded in epithelial cells and tube-casts. It seems that bile acids, although present in other fluids of the body, have never been demonstrated in the urine. According to Hofmeier, uric acid and urea are excreted in larger amount than by non-icteric children. The faeces are normal in colour and in other respects. They are never decolorised as in ordinary obstructive jaundice.

The diagnosis in uncomplicated cases presents no difficulty. The absence of serious symptoms, the slight degree of the jaundice, the pale urine, and the coloured stools suffice to distinguish even extreme instances of icterus neonatorum from cases of infective or catarrhal jaundice, and from those which depend on syphilitic disease of the liver, or congenital obliteration of the bile-ducts.

The prognosis is invariably good; no treatment is necessary.

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INFECTIVE JAUNDICE IN NEWLY-BORN CHILDREN.—This is of two kinds, according to the origin of the infection (*a*) from the Umbilicus, or (*b*) from the Intestine.

(*a*) **Infective Jaundice of Umbilical (or Puerperal) Origin** depends on infection, by streptococci or other organisms, which spreads by the umbilical to the portal vein, and thence to the liver. It may give rise to a perilobular cirrhosis, or set up an acute hepatitis with abscess formation, and it may end in general septicaemia. After death the liver is found of normal size, pale and bile-stained, and the ducts are pervious. There may be marked fatty change in the hepatic cells. Streptococcal inflammations of the pleurae, peritoneum, or meninges may be present.

The *symptoms* are local and general.—The *local* condition consists in suppuration about the umbilicus and often in redness and swelling of the neighbouring skin. It may be very slightly marked. According to Porak and Durante, apart from such serious conditions as erysipelas, phagedaenic ulceration, and gangrene of the navel, it may be said that the more marked the umbilical lesion is, the less severe is the general infection likely to be.

The *general symptoms* set in within the first two days. The child becomes irritable and sleepless, refuses the breast, vomits, and has green diarrhoea. The jaundice becomes increasingly marked, with more or less cyanosis and sometimes oedema ; and the temperature reaches 102-104° F. Haemorrhages may occur from the umbilicus or bowel, and are sometimes fatal. Within a few days, the baby may die in a comatose condition. When the general infection is severe the case is always fatal.

The *treatment* is mainly prophylactic, and consists in scrupulous attention to aseptic precautions in the management of the umbilical cord.

(b) *Infective Jaundice of Intestinal Origin* is a much commoner condition than that which starts from the umbilicus. It may occur in epidemics, or sporadically ; it is said to depend on *B. coli* and *B. lacticus* (Lesage and Demelin).

Morbid Anatomy.—After death all the tissues are bile-stained ; the liver is but slightly enlarged, and its section is either uniformly pale or shews alternating patches of pallor and congestion with haemorrhage. In some cases, it is in a soft, red diffuent state. The bile-ducts are normal. The spleen is usually normal in size, and of a brownish colour. The kidneys are congested. The intestine shews a slight degree of ordinary desquamative enteritis.

The *symptoms* set in rapidly without any apparent cause, the mother being quite healthy. The infant refuses the breast, vomits, and may have a slight convulsion. The disease rapidly reaches its height, and jaundice, marked cyanosis, and diarrhoea appear. The motions are not decolorised. The most marked feature is the cyanosis which varies from time to time in intensity, and is sometimes very pronounced. It may, indeed, mask the jaundice altogether, and it usually modifies its tint to a sort of bronze. The characters of the diarrhoea are important ; it is not severe and may therefore be overlooked ; at first there may be about three or four pale-green, alkaline or neutral motions in the twenty-four hours ; these are passed without any pain, the abdomen being soft and natural. In fatal cases, this condition of the stools continues till death. When the child begins to recover, however, the character of the motions changes ; they become more frequent (7-10), and are bright green in colour and acid in reaction. The general infection shews itself by drowsiness, slight fever, and emaciation. The duration of the case varies from three to twelve days.

The *diagnosis* between this form of infective jaundice and that from puerperal infection depends on the absence of an umbilical lesion, on the lower range of temperature, not much over 100° F. at the highest, and

on the absence of other infective lesions, such as pleurisy, peritonitis, and meningitis.

The *prognosis* is grave, the mortality being about 30 per cent. Severe cyanosis, high fever, and profound drowsiness are all unfavourable signs ; whilst the passage of an increasing number of highly bilious and acid stools is of good omen.

The *treatment* consists in attention to general hygiene, the administration of small doses of calomel, and especially in the use of subcutaneous injections of normal saline solution. Great care must be taken in the disinfection of the stools.

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CONGENITAL OBLITERATION OF THE BILE-DUCTS.—Description.—Under the heading of "Congenital Obliteration of the Bile-ducts" may be described a series of cases of infantile jaundice in which the bile-ducts and gall-bladder are found to be obstructed in a varying degree, and to shew signs of intra-uterine inflammation, while the liver is in a state of "biliary cirrhosis." The disease is comparatively rare, but more than one hundred cases authenticated by autopsies have been put on record.

Etiology.—No special hereditary disease has been observed in the parents of these cases. It is, however, remarkable that the disease frequently occurs in several children in a family. This must be taken into account in any attempt to explain its pathology. In only a few cases have malformations elsewhere been found. It is, however, important to note that there are several instances of multiple malformations on record in which obliteration of the bile-ducts or gall-bladder, or both, was present, which differed apparently in no important respect from the usual lesion (Witzel, Thomson (50), Pozzi). Two cases of congenital obliteration of the bile-ducts have also been published (Witzel, Feer), in which the viscera were transposed.

Congenital syphilis, it would appear, is not an essential element in the causation of this condition, although this has often been alleged to be so. We learn from a study of the published cases that—(1) Evidence of syphilis in the parents has very rarely been obtained—not in a twentieth of the cases ; (2) The brothers and sisters of the patients seem never to have shewn signs of it ; (3) In fifty-two infants living to be three months old and upwards, only twice were there noticed any of the symptoms which are usually attributed to congenital syphilis ; (4) Ordinary syphilitic lesions have scarcely ever been found post-mortem in patients who have died of this disease. A few cases are, however, recorded (Beck, Rolleston (40)), in which obstruction of the bile-ducts was certainly due to a syphilitic stricture.

Morbid Anatomy.—The degree of the lesion affecting the bile-ducts and the gall-bladder varies to a very large extent in different cases. In a few in which the patient has not lived more than a week or two, no disease may be visible to the naked eye, and no evident obstruction to the outflow of bile may be discovered; in others the walls of the ducts are markedly thickened here and there. In most cases, however, some portion of one or other of the ducts or of the gall-bladder has its lumen completely obliterated, and the fibrous tissue round it greatly increased in amount. Not infrequently parts of the affected structures have disappeared entirely, so that after death there is not even a strand of fibrous tissue to be found in their place. Extreme defects of this kind are most often found in patients who have lived for months; but sometimes this is the state even at birth. Enlarged and congested lymphatic glands are often, if not always, found in the neighbourhood of the bile-ducts.

The exact site of the obliteration, when present, also varies indefinitely, there seems to be no one place more apt to be affected than another. In some cases great dilatation of the duct occurs above the site of the obstruction.

The contents of the gall-bladder and ducts are by no means constant. If the child have lived more than a month it is usual to find colourless mucus only in the gall-bladder. Where coloured bile is present it is often described as unusually thick; in one case (Campbell) the common duct was blocked by an indurated cord-like plug of inspissated bile. In at least two instances (Bouisson, Thomson (51)) a gall-stone was found; and it seems quite possible that most, if not all, of the very rare cases of gall-stones in young infants may be examples of this disease.

Reports of microscopic examinations of the affected parts and the tissues in their neighbourhood are still much wanted. In one case (50) in which the gall-bladder was almost totally obliterated, its walls were found enormously thickened and infiltrated with young connective-tissue cells. What remained of the cavity, however, contained a recently desquamated layer of fairly normal cylindrical epithelial cells. In another case the duct near the point of obliteration shewed very considerable thickening of its wall, and disappearance of its muscular tissue, mucous glands, and epithelial lining (Rolleston and Hayne). In a recent case of my own a precisely similar condition was found.

The liver, when the child has lived for any length of time, is practically always enlarged. It is very tough in consistence, slightly uneven on the surface, and of a dark olive-green colour; on section it shews fine bands of fibrous tissue forming a network through it. Under the microscope the size and the consistence of the organ are found to be due to the presence of typical "biliary cirrhosis," and the green colour to innumerable small plugs of inspissated bile which distend the lesser ducts in many places up to their furthest ramifications; they may even occupy minute cavities within the liver-cells. The blood-vessels of the liver are normal in uncomplicated cases.

The pancreas seems not to have been very often examined. In two

cases (Feer, and Fuss and Boye) it was normal. In others (Cattaneo, Emanuel) some fibrosis is reported to have been present, and this was also found in a slight degree in a recent case under my care.

The spleen is usually much enlarged and fibrotic.

The peritoneum, in most cases, is quite free from traces of disease, either past or present; but occasionally ascites or purulent peritonitis has been found. In a few of the reported cases there were adhesions in the neighbourhood of the ducts implicating the blood-vessels; in almost all of these there was reason to suspect the presence of syphilis.

Pathology.—In considering the pathogenesis of this condition in the light of its morbid anatomy we are met by three questions, on which there is great difference of opinion: (1) What is the nature of the narrowing of the ducts if it is a primary condition? (2) What is the relation of the inflammatory changes in and around the ducts to the narrowing? (3) Are the changes found in the liver primary, or are they secondary to the obstruction of the ducts?

(1) As has already been suggested, the family occurrence of the disease, and its occasional association with numerous undoubtedly developmental malformations, make it very probable that the inflammatory changes present are secondary to some defect in the development of the ducts. The hypotheses that the ducts are not formed at all in the process of development (Legg, Skormin), or that they are solid and without any lumen from the first (Lotze), or that two outgrowths, from the duodenum and liver respectively, which should unite to form the normal ducts, fail in these cases to do so completely (Mohr), are none of them, as Beneke points out, in accordance with modern views of embryology. Beneke favours the hypothesis that the bile-duct becomes constricted in the progress of development. He supposes that there is an abnormal proliferation of the cells lining the bile-duct near the duodenum in early intra-uterine life; and that, as the duct elongates, this catarrhal process leads to a narrowing of its lumen. Lavenson also supports the view that the obliteration of the bile-ducts is due to a developmental abnormality.

(2) The lesions of the ducts and gall-bladder certainly indicate that there has been chronic progressive inflammation. This is probably secondary to pre-existing narrowing of the duct, but when the duct becomes absolutely obliterated it is always due to inflammatory action. It seems probable that the inflammation in and around the ducts is caused by the presence of some irritating property in the bile.

(3) With regard to the connexion between the hepatic cirrhosis and the lesion of the ducts two different views are held. Dr. Rolleston (41) believes that the disease really begins in the liver, as a mixed cirrhosis and cholangitis set up by poisons conveyed to it from the mother. The cholangitis accounts for the jaundice, and passing down into the larger extra-hepatic bile-ducts it induces in them an obliterative inflammation analogous to obliterative appendicitis. Dr. Emanuel has recently advocated a similar view. According to the older hypothesis, to which I

adhere, the obstruction to the lumen of the ducts is always the primary, and the cirrhosis of the liver a secondary lesion. When the disease in the ducts has gone far enough by the time of birth to cause interference with the free passage of bile from the liver, "biliary cirrhosis" begins, as it does in the liver of animals whose common duct has been tied (Charcot and Gombault); and the amount of glycogen is diminished (Legg). This causes an increasing interference with those important functions of the liver by virtue of which it protects the organism from the dangers of auto-infection (Roger). Any fermentation in the new-born child's bowel will, therefore, in these circumstances set up hepatic cirrhosis much more readily than it would under normal conditions (Boix).

On reconsideration of the morbid anatomy and from study of recent literature on the subject I am inclined to return to the view I formerly held (49), as to a relative narrowing of the bile-duct of developmental origin being probably the primary cause of all the other changes. This view, as further elaborated by Dr. L. S. Milne,¹ seems to me to afford the most probable account of the pathogenicity of cases of congenital obliteration of the bile-ducts. The order of events according to Dr. Milne's hypothesis is somewhat as follows:—There is, to begin with, a congenital narrowing of the bile-duct of developmental origin, possibly produced as Beneke describes. This may be slight, but it is sufficient to cause stagnation of bile in the liver. The stagnation results in the retention of metabolic products which are arriving at the liver both by the umbilical vein and by the hepatic artery. The elimination of these accumulated products by the bile causes it to become more irritating in character, so that it sets up local inflammatory changes in the already narrowed ducts and so leads in time to their complete obliteration. The continued arrival at the liver of accumulated toxic products, acting along with the stagnation of irritating bile, also damages the liver substance, producing necrosis and resulting cirrhosis. At first, in spite of this, the liver, by means of the lymphatic circulation, is able to carry on its work as a toxin filter; for, in the fetus, the organ has comparatively little of this to do. This is owing partly to its being protected by the action of the placenta, and partly to the absence of putrefactive processes in the bowel. Later, however, when the intestine is more used, the inadequacy of the liver's protective action becomes increasingly important, toxic products correspondingly accumulate, and the child eventually dies from toxic poisoning. To this are due such symptoms as the vomiting, spontaneous haemorrhages, and convulsions. The liver of the fetus being less accustomed to the action of toxins is more apt, than it would be in later life, to be deranged by the occurrence of toxæmia, and more liable to suffer from cirrhosis. On this hypothesis the fibrosis of the pancreas and spleen is readily explicable.

Clinical Features.—The parents of the patients seem generally to have been healthy people, and yet, in a considerable proportion of the cases, it is found that they have previously had one or more infants

¹ Dr. Milne's views have not been published as yet, but he allows me to mention them here.

similarly affected. In some instances as many as seven or even ten cases of infantile jaundice, apparently of this nature, have occurred in one family. Boys are affected more frequently than girls (41 : 26).

At birth the child appears normal and well nourished, and nothing attracts special attention to it until either the whiteness of the stools or the yellow discolouration of the skin is noticed.

The jaundice is always a very marked feature, but the date of its onset varies considerably. Sometimes it is present at birth, often it is not noticed until the second or third day of life, occasionally it does not set in until the ninth, tenth, or even fourteenth day. When first observed the yellow colour is slight in degree, but within a day or two it noticeably deepens, and soon becomes of a dark greenish-yellow hue. It remains until death; it may, however, vary a little in intensity from day to day, and, if the child live for some time, the tint is often paler during the last few weeks.

It is to be observed that in those cases in which only one of the hepatic ducts is obliterated, and also in those in which all the ducts seem pervious, the jaundice may be just as severe as in those with complete obstruction of the common duct. In some cases a quantity of dark, apparently normal meconium is passed in the usual way, and is followed at once by colourless motions; in others the faeces are devoid of colour from the very first. Rarely are any yellow faeces passed, but after a dose of mercury the stools may be partially greenish for a time. The bowels are generally costive. The urine is deeply bile-stained.

The occurrence of spontaneous haemorrhages in various situations is a very characteristic symptom. A considerable number of the children suffer from bleeding at the navel, a symptom which usually sets in shortly after the separation of the cord (fifth to ninth day). It is of the nature of a general oozing from the raw surface, and is exceedingly difficult to stop; indeed it almost invariably results in death within two or three days at the furthest. Of those patients who survive the first fortnight a large number suffer from spontaneous bleeding from other parts, such as sub-cutaneous ecchymoses or epistaxis; or the blood may be vomited, or passed with the motions. If the children are not carried off by haemorrhage or some other such cause during the first week or two, they generally live from three to eight months. It is interesting, however, to observe that in those instances in which more than one child in a family is affected the tendency to haemorrhage is particularly strong, and the patient scarcely ever survives the first fortnight.

Towards the end of the case there is more or less emaciation; but the interference with the general nutrition is usually much less than might be expected from the gravity of the lesion. Fits not infrequently come on, and, in the exhaustion of approaching death, some intercurrent disease, perhaps of a trifling kind, brings life to a yet earlier close.

The diagnosis may present some difficulty at first, but within a few days the deepening jaundice, colourless motions, and bile-stained urine render it evident that there is something more serious the matter than

ordinary icterus neonatorum. Moreover, the comparatively slight effect produced at first upon the child's general health readily distinguishes these cases of jaundice from those associated with umbilical phlebitis and like infective conditions, and also from the rare syphilitic cases.

As the child grows older the occurrence of spontaneous haemorrhages and the gradual enlargement of the liver and spleen strongly confirm the diagnosis.

The prognosis is, of course, of the utmost gravity; no child proved to have this complaint has ever lived eleven months. It should be mentioned, however, that a few cases of infantile jaundice have been reported as ending in recovery which, from their symptoms, and from their occurrence in the same families as other children with obliterated bile-ducts, seem possibly to have been cases of this disease (Anderson, Freund, Grandidier).

Treatment.—Our ignorance of the causation of the disease, and its commencement during intra-uterine life, put curative treatment out of the question in the only stage at which it could possibly be of any avail. In several cases (16), (34), (37), (53) the abdomen has been opened during life in the hope that, if the obstruction were situated low down, it might be possible to re-establish communication between the bile-channels and the intestine. This was not found practicable; and the pathology of the disease certainly gives us no encouragement to expect even temporary relief from any surgical procedure.

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WEIL'S DISEASE

By WILLIAM HUNTER, M.D., F.R.C.P.

SYNOMYS.—*Infectious Jaundice; Febrile Jaundice.*

IN 1886, under the title of "A Peculiar Form of Acute Infectious Disease characterised by Jaundice, swelling of Spleen, and Nephritis," Weil of Heidelberg described four cases of febrile jaundice presenting certain general features of resemblance. He was in doubt whether to regard them as extremely rare modifications of other well-known forms of infectious disease, or as a hitherto unrecognised disease. The paper excited much interest, chiefly amongst German observers, who decided at once in favour of the latter alternative, and gave it the title of Weil's disease.

Since then a considerable discussion has sprung up in connexion with the subject—especially amongst German writers. French observers have, for the most part, declined to see in the condition anything more than what they had long been accustomed to describe under the title of *icterus gravis*, or infectious jaundice. This opinion has been shared by most English writers, and has been endorsed by Dr. Sandwith with regard to the identity of the infectious jaundice in Alexandria, Smyrna, and the Mediterranean with Weil's disease.

Etiology.—The disease has been most commonly met with in men between the ages of fifteen and thirty; some estimates give the percentage of males as 90 per cent; a few cases have occurred in children between eight and fourteen, and Brüning reported a case in an infant four months old. The greatest number have occurred in the summer months between June and September, but isolated cases have been met with in winter and spring.

It is not confined to any one class of society, but it is certainly most common in working-men whose occupations or habits have exposed them to insanitary surroundings.

Infection undoubtedly plays the most important part in producing it. The consumption of tainted meat has been incriminated in a number of cases (Schmidt, Leick). Thus, out of 13 cases recorded by one observer (Fiedler), 9 were in men engaged in the slaughter-house of Dresden, and two of the others had eaten tainted sausage. Two cases described by another observer (Stirl) were in workmen engaged in cleaning out a sewer. Ducamp reports on a slight epidemic outbreak of infectious jaundice in six workmen who fell ill after cleaning out a blocked sewer, three of them of gastric catarrh, three of Weil's disease. Lastly, a series of epidemic outbreaks of the disease have been recorded, chiefly by garrison officers in Germany.

Thus, under the title of "infectious jaundice" an outbreak of jaundice was recorded in 1866 by Weiss,—25 cases observed by himself, and 15 others known to him,—presenting in all respects the characters of Weil's disease. In one instance a father and two sons were attacked successively. Similar outbreaks have been recorded by Haas (1887) and Weiss (1889), both in Prague; and by Pfuhl (1888), Hueber (1890), and Jaeger (1892). The last observer has reported 9 cases—three of them fatal—occurring in garrison at Ulm; the source of infection was traced by him to bathing in a certain part of the river near the garrison. A similar outbreak in a garrison was traced to bathing, and reported by Globig (1890). Outbreaks were described in South Africa during the Boer War of 1899-1902.

Pathogeny.—As to the nature of the infection further observations are desirable. Jaeger succeeded, in 2 out of 3 fatal cases, in discovering within the organs of the body a certain organism, with definite morphological and cultural characters, which he believes to be the cause of the disease. He found this organism, *Bacillus proteus fluorescens*, in the urine in four out of six of the patients who recovered, whereas he failed to find it in a case of simple catarrhal jaundice. On further investigation he ascertained that on the banks of the infected river running past the garrison where the disease was acquired by bathing, the ducks and geese were subject to a fatal disease marked by jaundice, and on examination he found the same post-mortem changes and the same organism present in them. In two fatal cases recorded by him Nauwerck (1888) found organisms in the intestinal wall—partly within the glands, partly amidst the connective tissue—apparently within widened lymphatics, and forming zoogloea-like masses made up of small bacilli with rounded ends deeply stained, the middle portion being hardly stained at all. Jaeger recognised in the description the same organism he also had found. These observations have been confirmed in America by Libman, Brooks, and Satterlee.

Morbid Anatomy.—The disease is not usually fatal; and hence only a few records of post-mortem examinations are available, such as three

recorded by Sumbera, two by Nauwerck, one by Brodowski and Dunin, three by Jaeger, and one by Brooks.

The following was the condition observed by Sumbera in 3 fatal cases. In all there was jaundice with fatty change in the heart-muscle, and numerous punctiform haemorrhages either under the skin, the pericardium, the pleurae, or the mucous membrane of intestine.

Three fatal cases have been recorded by Jaeger. The chief changes were jaundice; fatty degeneration of liver with indistinctness of lobules, and small-celled infiltration of connective tissue; fatty degeneration and cloudy swelling of the renal epithelium and acute parenchymatous nephritis; minute haemorrhages in different organs; swelling of spleen; intestinal changes, observed in one case only, but in this one very notable, namely, marked vascularity, numerous haemorrhages, and superficial erosions of mucous membrane throughout the whole intestinal tract. No trace of typhoid lesion was ever observed. In 2 out of the 3 cases Jaeger found a definite organism in the tissues as already noted. Similar changes were described in the 2 cases by Nauwerck (1881). The changes in the liver are described by him as resembling those of acute yellow atrophy in many respects; liver-cells reduced to a granular fatty detritus; the epithelium of the bile-ducts shewing fatty change in a high degree.

Nature and Relation to other Forms of Jaundice.—The infective nature of the disease can hardly be doubted. The sudden onset and the character and course of the symptoms suggest this; and its occasional occurrence in epidemic or endemic outbreaks seems to establish it conclusively. Beyond this its etiology is quite obscure; how much so may best be judged from the different names given to the condition by different observers. Weil gave it no name at all. He was not sure whether to regard it as a special disease, a form of "biliary typhoid," or as a form of abortive enteric fever. And on these points the opinions of German observers appear greatly divided—"Infectious or septic jaundice" (Fraenkel); "Febrile jaundice" (Wagner); "Infectious jaundice" (Wasilieff, Weiss); "Icterus typhosus" (Heitler); "Abortive enteric fever" (Haas); "Typhus bilius nostras" (Weiss).

The term "biliary typhoid" has been given to it on the ground that its characters agree generally with those formerly described by Griesinger under the name "typhus biliosus." Moreover, it has been thought to be identical with the disease described as "typhus biliosus or icterodes" met with in Alexandria and Smyrna. The name appears to me, however, to be particularly inapplicable. For later observers have shewn that the disease described by Griesinger was really relapsing fever; in which disease jaundice occurs in a large proportion of cases [Vol. I. p. 1182]. And there are important differences between it and the Smyrna disease; in the latter the spleen is usually normal, parotitis is common, and over 27 per cent of cases prove fatal.

The disease cannot be regarded as an abortive form of enteric fever. Jaundice is one of the rarest complications of enteric fever. Murchison

met with only 4 cases ; Jenner never with one ; Liebermeister with 26 out of 1420 cases ; Griesinger with 10 out of 600 cases. Moreover, when jaundice does occur it is not, as in the condition now under consideration, at the outset of the disease. Lastly, in the necropsies recorded typhoid lesions have not been noted ; and although, as in other forms of jaundice, the blood-serum may clump *Bacillus typhosus* even in dilution (Eckhardt) this is not constant.

These possibilities being excluded, there remains only the question whether the condition is to be regarded as a special disease, or as one form of "infective jaundice." The evidence appears to me to be against the former and in favour of the latter view.

The closest relations of the disease appear to be with other forms of "infective" jaundice such as are met with sporadically or endemically both in this country and abroad, and more especially with sporadic forms of yellow fever in America.

Neither in the symptoms nor in the morbid changes described as Weil's disease is there anything essentially characteristic. They are those of a severe icterogenous poison, more severe than that found in epidemics of ordinary catarrhal jaundice, and in most cases not so severe as that observed in cases of "malignant" jaundice (*icterus gravis*). Its relations to both these varieties of jaundice are, however, manifest. Thus, I find 4 cases recorded (von Fetzer, 1882) amongst soldiers, three in August and one in September, in certain rooms of a barrack in which there had been an outbreak of epidemic (catarrhal) jaundice from February to June of the same year ; one of those attacked in August having suffered from "catarrhal" jaundice in June. On the other hand, the symptoms and post-mortem appearances in severe fatal cases are absolutely indistinguishable from those of severe cases of *icterus gravis*. In two of Jaeger's cases even tyrosine crystals were found in the urine.

It appears to me, then, that until the nature of the infecting agent can be determined, no advantage is to be gained from regarding a condition which probably owes its origin to different infective agents in different localities as a special disease, or in giving to it the name of any one observer. The older name of "infectious jaundice" serves sufficiently to describe it.

As regards the character of the jaundice itself, it remains to point out that there is a striking similarity between it and that producible experimentally in dogs by toluylenediamine. Great swelling of spleen and liver and nephritic changes are constant features of the action of this drug. When large doses are given I have found that considerable fever is also present. Post-mortem the changes are identical, the bile-ducts being distended with bile ; and, most striking of all, the duodenum shews in certain cases the marked congestion which I have described as characteristic of the action of toluylenediamine.

Symptoms.—The character of the disease in Weil's original cases was that of a sharp febrile attack coming on suddenly, with or without rigors,

followed on the second or third day by jaundice, swelling of liver and spleen, and nephritis ; marked by severe nervous symptoms, and ending gradually in recovery about the tenth or fifteenth day.

The disease begins with fever with or without rigors, extreme debility and general malaise, painful sensations or violent muscular pains in the back and limbs, loss of appetite, thirst, usually diarrhoea, headache, giddiness, and disturbed sleep. These symptoms increase in intensity for a day or two, the weakness becomes more marked, and to the other nervous disturbances there are added slight delirium and somnolence. On or after the third day jaundice appears, with marked swelling and tenderness of the liver and enlargement of the spleen ; and the urine becomes albuminous, and shews the other changes characteristic of nephritis. In the digestive system the disturbances are well marked—furred tongue, sometimes vomiting, diarrhoea, or constipation, sometimes abdominal pains and uneasiness.

All these symptoms continue for two or three days more, and then gradually subside, improvement setting in on the fifth to the eighth day. The temperature, which has remained high, falls gradually to the normal about the tenth day, the jaundice gradually disappears along with the other symptoms, and convalescence begins.

The convalescence may be uninterrupted ; but in a certain number of cases, according to Quincke in 40 per cent, after an apyrexial period of one to seven days, fever recurs, lasting five or six days, and usually attended with recurrence of jaundice, swelling of liver and spleen, and albuminuria.

Convalescence is in all cases slow, the patients being left much reduced in strength for many weeks after.

The jaundice lasts about fourteen days, and disappears slowly. Bile pigments are abundantly present in the urine ; bile acids are also sometimes present. It is attended by *swelling and tenderness of liver*, corresponding in degree to the degree of jaundice, and gradually disappearing with the latter.

In all cases there is also notable *enlargement of the spleen*, recognisable at the very outset of the fever even before the jaundice appears, and lasting as long as the fever lasts.

The fever is a constant symptom and is usually high, reaching 103° or 104° F. in the course of the second or third day, and, with slight morning remissions of about a degree, it remains high for several days. Then between the fifth and ninth days it begins slowly to fall, and reaches the normal about the ninth or twelfth day.

The pulse corresponds to the fever, is usually rapid—110 to 120, sometimes even 136. When jaundice appears it becomes slower.

Nervous symptoms are very prominent and constant. They include headache, giddiness, great prostration, and more or less delirium. But perhaps the most striking symptom of all is the muscular pains, especially in the calves of the legs ; these are sometimes so severe that they put the other subjective symptoms into the background. The pains occur

spontaneously, and are greatly increased by movements and by palpation of the muscles.

Nephritis is almost constant, and is evidenced by albuminuria, presence of epithelial casts, and sometimes blood. Its occurrence coincides with the enlargement of the spleen, and it usually subsides with the latter. Some albuminuria often persists for a long time during convalescence.

Occasional symptoms observed have been *rashes*, *roseola*, *erythema*, *purpura*, *herpes*, and in a few cases *epistaxis*.

Diagnosis.—The distinction from relapsing fever, which resembles it in several particulars—the jaundice and the liability to relapses—can be made by examination of the blood, which is sterile in Weil's disease, and shews the *Spirochaeta obermeieri* in relapsing fever. The diagnosis from enteric fever has been incidentally referred to. Mild cases of yellow fever are much like Weil's disease.

Prognosis is generally good. In Alexandria the mortality has varied from 10 to 60 per cent (Sandwith). In 44 cases in Germany there were 5 deaths.

Treatment consists in rest in bed, a milk diet, and mild intestinal antiseptics by the mouth. Copious enemas of water have been recommended.

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ACUTE YELLOW ATROPHY OF LIVER

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SYNOMYS.—*Ictère grave, Icterus typhoides* (Lebert), *Akute parenchymatöse Hepatitis* (Foerster), *Ictère hémorragique essentiel*, *Parenchymatöse Degeneration der Leber* (Liebermeister).

Definition.—An acute disease, probably of toxic origin, characterised by jaundice in association with severe cerebral symptoms, black vomit, and haemorrhages; and by extreme diminution in the size of the liver due to parenchymatous degeneration.

History.—The disease was probably not unknown to earlier writers, but only a few cases, and these of doubtful nature, are recorded until the last century, no account of any case, according to Dr. Wickham Legg, being found earlier than 1616. One of the first to describe cases presenting the features of this disease was Morgagni. Early in the nineteenth century observations were made by the Dublin physicians, Cheyne (1818), O'Brien (1818), and Marsh (1822); and in Edinburgh by Abercrombie (1828). One of the earliest and fullest descriptions of the disease, however, was that given by Bright (1836), whose account must be regarded as the first recognition of the disease as a definite symptom-group. He described it as a diffuse "inflammation" of the substance of the liver affecting the glandular substance more than the connective tissue, leading frequently to marked diminution in the size of the organ, causing jaundice associated with severe nervous symptoms, and a special tendency to haemorrhage.

The history of the disease, under the title it now bears, dates from 1843, in which year Rokitansky, basing his description mainly on the naked-eye appearances presented by the organ, described it under the name acute yellow atrophy. A few years later the characteristic microscopic appearances, significant of degeneration of the liver-cells, were described; first of all by two English observers—Busk (1845) and Handfield Jones (1847). In France the first full account of the disease was given by Ozanam (1849), under the title of a "forme grave de l'ictère essentiel."

From this time onward observations accumulated. Lebert's study of the disease (1854) was based on 72 recorded cases of *icterus gravis*, many of them of doubtful nature. He regarded the condition as a general disorder rather than as a special disease of the liver, and preferred to name it *icterus typhoides*; this view was propounded about the same time by Buhl also. In the first edition of his well-known work on *Diseases of the Liver* (1858), Frerichs based his account of the disease on a study of 13 cases which had come under his own observation, and 31 recorded

cases. The similarity between the morbid changes found in the liver and kidney in this disease and those produced by phosphorus poisoning was first pointed out by Rokitansky (1859). Later important contributions to the study of the disease were made by Wunderlich (1860), Wagner (1862), Liebermeister (1864).

Wagner was the first to suggest that many cases of the disease might really be unrecognised cases of phosphorus poisoning. Liebermeister described 10 cases observed by himself, and made a study of all the cases of icterus gravis on record (177 in number recorded by eighty-two authors), fitted to throw any light on the relation between that condition and acute yellow atrophy. In 1880 appeared the works of Dr. Wickham Legg and Thierfelder, the former based on the study of 100 cases recorded up to 1876-77, and the latter on 143 cases recorded up to the same date.

Etiology.—Acute yellow atrophy must be ranked among the rarest of diseases. It is seldom met with even in the largest hospital practice. Out of 25,700 cases admitted during nine years into the London Fever Hospital at a time when a brown tongue and delirium constituted a sure passport to admission, Murchison only met with one case. At the Johns Hopkins Hospital, Baltimore, there have been 3 cases only (Thayer). Four cases have come under our own notice. In 1880 Thierfelder estimated that the total number of recorded cases was about 200; in 1895 one of us (W. H.) collected 50 additional cases, in 1899 M'Phedran collected 29 more, and in 1903 Best estimated that the total number recorded came to about 500.

Age.—One-half of the cases of acute atrophy have been met with between the ages of twenty and thirty, but no age is exempt. It is very rare in childhood below the age of ten; out of 343 cases collected by Thierfelder, Wickham Legg, Lebert, and Hunter, 21 occurred in patients under that age. Skormin quotes 7 recorded cases in new-born infants. Below ten and above forty the number rapidly diminishes.

Sex.—The influence of sex is undoubtedly, females greatly preponderating among those attacked. Between the ages of twenty and forty, when the liability to the disease is greatest, the proportion of females to males attacked is exactly double. This greater liability is connected with the occurrence of pregnancy. Out of 164 cases in women collected by Thierfelder, Frerichs, Wickham Legg, and Hunter, 66 were pregnant or suckling. The resistance of the liver appears to be low in this condition, for epidemics of catarrhal jaundice are particularly fatal to pregnant women. Thus, in the epidemic which occurred in Martinique in 1858, reported by Gallot, these were the only severe sufferers, and no fewer than 20 died after abortion. The toxæmic vomiting of pregnancy is frequently accompanied by degenerative lesions of the liver, and many cases have been observed to terminate in acute yellow atrophy. Indeed, since all gradations have been observed between the two conditions, both in the clinical picture and in the pathological changes, it has been asserted by Stone, and by Ewing and Wolf, that they are the same disease.

Acute yellow atrophy has been observed as early as the sixth week of pregnancy (Whitridge Williams), but is most common in the second half. Even in pregnant women, however, the disease is very rare—one in 28,000, according to one observer (Braun), or 2 in 33,000 (Spaeth).

Syphilis.—In a small proportion of cases a definite relation has been found between syphilis and acute yellow atrophy, which appears to follow upon the mild jaundice occasionally observed in the secondary stage. Dr. Rolleston has collected 28 cases of post-syphilitic acute atrophy of the liver, and points out that this condition is probably to be regarded as an acute degeneration terminating a pericellular cirrhosis.

Alcohol.—In a certain number of cases—in 13 out of Thierfelder's 143—the disease occurred in patients who were or had been heavy drinkers; and in 6 of the 13, the attack had followed a period of unusually heavy drinking. As pointed out by Liebermeister, the habitual use of alcoholic drinks favours a certain degree of parenchymatous degeneration of the liver.

Acute yellow atrophy has occasionally been observed to follow an operation and has been ascribed to shock. It is possible that some of these cases were due to the action of chloroform upon the liver. Even in health, the administration of chloroform in animals can cause, if repeated, an acute necrosis of the liver.

Other Hepatic Diseases.—The disease occurs not only primarily, as an acute process in persons previously in good health, but also secondarily in persons already the subject of liver disease. Cases are recorded in which it occurred secondarily to, or was superadded to, cirrhosis of the liver, long persistent biliary obstruction, or chronic fatty change; but there is no evidence that these morbid conditions—which after all are relatively very common—have any special causative relation to the disease, except in so far as they induce an unhealthy state of the liver-cell, or reduce the amount of liver tissue (cirrhosis). It must, however, be remembered that some fibrosis of the liver is to be expected in prolonged cases of acute yellow atrophy. We have already referred to pregnancy and syphilis as disposing causes. No line can be drawn between these instances of acute yellow atrophy added to pre-existing disorder of the liver of various kinds, and the class of cases included under other varieties of *icterus gravis*.

Mental Emotion.—That an antecedent morbid condition of the liver-cell is, however, not necessary for the occurrence of the disease is clear, because in the majority of cases it attacks people previously in robust health; and in a considerable proportion of these the only cause assignable has been the influence of fright or some depressing emotion. Out of Lebert's 72 cases, 13 were assigned to the latter cause; as were 16 out of 100 collected by Dr. Wickham Legg; and one-tenth of the cases according to Thierfelder. Most of these were in women. On the basis of such cases some authors surmised that acute yellow atrophy is a nervous disease (von Dusch), or at any rate that depressing emotion

plays a pre-eminent part in its causation (Liebermeister). It must be remembered, however, that the pregnant condition, during which a considerable proportion of the cases occurring in women arise, is often accompanied by emotional disturbance. Among recent cases two only are ascribed to mental shock,—one in a pregnant woman aged twenty-four (Hayward, 1890); one in a man aged forty-one (Duckworth), who saw his own child run over in the street; on the following day he became jaundiced, and four weeks later the acute symptoms set in.

Toxic Influences.—It is when we come to discuss the relations of acute yellow atrophy to other forms of severe jaundice that we find some light thrown on the probable etiology of the disease. The symptoms shew such a general resemblance to those of phosphorus poisoning that some observers have regarded cases described as acute yellow atrophy as really due to undetected phosphorus poisoning. The differences between these two conditions, described below, together with the absence of any evidence of ingestion of phosphorus in most cases of acute yellow atrophy, shew that phosphorus poisoning and acute yellow atrophy are not identical; nevertheless, they resemble each other so closely as to indicate that the latter like the former is due to the action of a powerful poison.

Further support is lent to this opinion when we consider the close affinities between this disease and other forms of severe jaundice, in which the action of specific poisons is undoubtedly; such, for example, as yellow fever. The resemblances between yellow fever and acute yellow atrophy are many and striking, so as even to suggest to some observers that the latter may be nothing more or less than sporadic cases of the former.

And so it is with regard to other forms of severe jaundice—*icterus gravis*—whether occurring sporadically or in epidemic form. Many such outbreaks of *icterus gravis* have now been recorded, by Budd, Graves, Carville, and others, sometimes widespread, sometimes limited to a single household; and the more severe of these present many of the features of acute yellow atrophy, including the nervous disturbances, the haemorrhages, and the disintegration of the liver tissue in fatal cases.

Amongst the 44 recent cases of acute yellow atrophy collected by one of us (W. H.), no fewer than 9 (all in pregnant women) are recorded by three Australian observers in districts where epidemic outbreaks of jaundice seem comparatively common (Broken Hill Proprietary). Two of these cases, carefully described by Creed and Scot-Skirving (1889), occurring at 8 and 8½ months of pregnancy respectively, are especially worthy of note, inasmuch as they presented all the clinical features of acute yellow atrophy, including diminution of liver dulness, yet ended in recovery. In one leucine and tyrosine were present in the urine, in the other the symptoms included severe nervous phenomena, petechiae over the limbs and trunk, and coffee-ground vomit.

The resemblance between acute yellow atrophy of the liver and fatal cases of *icterus gravis* is thus exceedingly striking. It extends not only to the clinical features and course and morbid anatomy, but

also to the occasional endemic characters of the former disease. The resemblance is so striking as to render it probable that, in the one as in the other, toxic influences or agencies are at work; this presumption is the stronger in icterus gravis on account of its comparatively frequent occurrence in endemic and even in epidemic form. Of what nature these toxins may be, we know as yet nothing.

In arriving at this conclusion, which appears to be most in consonance with the data, it is not necessary to press it so far as to assume that the toxic agencies are specifically the same, and different only in degree. On the contrary, the occasional occurrence of acute yellow atrophy in endemic form, as in the cases above described, lends support to the view that it is a specific form of icterus gravis.

Morbid Anatomy.—The chief change is presented by the liver. This is reduced in size, sometimes to a great degree, and is found lying collapsed with smooth surface and wrinkled capsule, fallen away from the ribs in the right hypochondrium. Both on the surface and on section it shews a number of orange-yellow patches of varying size and outline, distributed irregularly through its substance; in these areas the lobules can only be made out with difficulty. The remainder of the liver is of reddish colour, of uniformly soft consistence, and its lobules are indistinguishable. The red areas, usually more marked in the left lobe, are those in which the degenerative process is most advanced, the capillaries being exposed by the destruction of the parenchyma. Small haemorrhages may be present under the capsule. The larger bile-ducts contain mucus only; the gall-bladder frequently contains some bile.

The reduction in size is variable, but amounts on the average to one-third or more. In 28 adult cases collected by one of us (W. H.), in which the weight of the liver was recorded, in 5 it was below 30 oz. (the average normal weight being 50 oz.), in 19 between 30 and 38 oz. It has been suggested that the size of the liver depends upon the duration of the disease, that it is large at an early stage and small later. In our opinion the facts lend no definite support to this opinion, for, even in patients who have died four days after the first symptoms were noticed, the liver has been found much reduced; and in a case recorded by Sir W. Church, in which the duration of the disease from start to finish was five days, the liver weighed only 32 oz.

In some cases the disease does not prove fatal or is prolonged for many months, and when an opportunity of examining the liver is afforded, evidence of the destructive process, and also of regeneration, may be found. Compensatory hyperplasia, due to proliferation of the cells of the liver and bile-ducts, may give rise to nodular masses resembling adenomas. These regenerative changes have been specially investigated by Marchand, Meder, Stroebe, W. G. MacCallum, and Muir.

The appearances on *microscopical examination* vary in different cases and in different parts of the liver, according to the degree of necrosis. In the yellow areas the cells are swollen and shew some fatty change. As will be seen later, analysis shews that there is no or very little

increase in the amount of fat in the liver. The appearance of droplets is due to the fat becoming more visible. Apparently this is characteristic of an early stage of poisoning of the liver-cells, for Saxl has recently shewn that when phosphorus is injected into the portal vein the first effect of the poison is to cause fat to become microscopically obvious, without any increase in its quantity. The nuclei stain badly and are observed to be breaking down, whilst the cytoplasm is granular and contains small quantities of bile.

These degenerative changes usually begin in the periphery of the lobule and advance towards the centre (Rolleston). In some cases, and constantly in those occurring as a sequel to the toxæmic vomiting of pregnancy, the change begins in the centre of the lobule. The cells lining the bile-ducts proliferate, break down, and block the ducts, causing jaundice.

In the red areas the liver-cells have disappeared, a frame-work of the stroma and capillaries being left, containing fragments of nuclei and red cells. At the periphery of the lobules attempts at regeneration may be seen to take place from the bile capillaries in the less acute cases. Liver-cells shewing karyokinesis arrange themselves in rows, and in cases of longer duration give rise to the above-mentioned nodules of newly formed tissue which project on the surface of the liver. The region of the portal canals is also often the seat of a small-celled infiltration.

On *chemical examination*, the liver has been found to contain a large number of the products of hydrolysis of protein. Leucine and tyrosine have long been known to be present in the liver in many cases. Prof. Gamgee in 1881 estimated that there were 10·8 grains ('7 grams) of leucine and '56 grains ('04 grams) of tyrosine in the whole liver. A. Taylor (1902) obtained '35 grams of leucine and '6 of aspartic acid. A thorough analysis of the liver by modern methods has recently been made by H. Gideon Wells in a case of a young man who died six weeks after the onset and two weeks after the symptoms became severe. A considerable amount of disintegration of protein had taken place, with the formation of histidine, lysine, leucine, tyrosine, glycocoll, alanine, proline, glutaminic acid and aspartic acid, xanthine and hypoxanthine, a sulphur-containing compound, and small quantities of proteoses and peptone were also found. Nearly a third of the nitrogen was in a water-soluble non-protein form.

This condition shews a striking resemblance to the self-digestion or autolysis of cells, which occurs after death or when the circulation is arrested during life, by the proteolytic and other ferment contained in all tissues. This autolysis is doubtless always going on, but in health new material is brought to the cell to make up what is lost, and autolysis is held in check by the alkaline reaction of the tissues, and probably by anti-ferments contained in the blood serum. The chemical products of the autolysis of the liver are precisely those detailed above as occurring in acute yellow atrophy. It appears, therefore, that in this disease the toxic influence acts on the liver in such a way as to inhibit

the recuperative powers of the cells, and, probably by diminishing the alkalinity of the tissues, sets autolytic ferments free to break down the bioplasm. The composition of the insoluble proteins remaining in the liver is unaffected. The proportion of lecithin is diminished; no free lactic acid or volatile fatty acids are found. The percentage of fat is normal. There is a considerable increase of phosphorus, attributed to the cleavage of nuclein bodies, and of iron due to deposition of blood pigment. The yellow colour of the tissue is due to bilirubin, and turns green upon immersion in an oxidising agent such as potassium bichromate; the proportion of water in the liver, normally about 70 per cent, is increased.

Micro-organisms have been sought for, but usually with negative results. Bacteria and micrococci have been described by Klebs in three cases in the large and small bile-ducts, and in the interstitial connective tissue. Dreschfeld in one case (that of Tomkins), examined half an hour after death, found numerous large micrococci in the portal canals filling the arteries and capillaries, especially in the peripheral part of the lobules where the liver-cells were either intact or only beginning to be diseased.

The spleen is enlarged in rather more than half the cases and is soft; and sometimes this enlargement is recognisable during life.

The kidneys are bile-stained, and shew degeneration of the epithelium of the convoluted tubules.

Haemorrhages are present not only under the skin, but scattered about the mesentery, the pericardial and pleural surfaces, the mucous membrane of the stomach, the pelvis of the kidney, and the bladder, meninges and brain.

Pathogeny.—The nature of this rare disease is still for the most part obscure. It may be (i.) a primary disease of the liver—an acute inflammation leading to destruction of the secreting structure; or (ii.) a general constitutional disease to which the autolysis of the liver is only secondary; or (iii.) a rare form of infective disease, to be classed with other forms of jaundice produced by infective agents.

(i.) In favour of the first proposition is that the most obvious morbid changes have their seat in the liver; and that the characteristic symptoms of the disease appear to be directly related to this organ rather than to any other.

(ii.) In favour of the second proposition, it has been pointed out that not the liver only, but other organs—the kidneys and the heart—are found degenerated.

(iii.) In favour of the last alternative—that we are dealing with a rare form of infective disease—is that cases indistinguishable from acute yellow atrophy of the liver occur during outbreaks of severe epidemic jaundice; and that generally the symptoms and course of the disease, even in minute particulars, are similar to those met with in what is called malignant jaundice. An extensive epidemic outbreak of jaundice which occurred in Saxony and Dresden in the autumn of 1889 has been

recorded by Meinert ; no fewer than 518 persons were attacked. There were two stages in the disease : an initial febrile stage with rigor, sickness, headache, but without jaundice ; and a second stage of jaundice without fever, the fever falling on the second or third day, and the jaundice appearing on the fifth or sixth day, and lasting on an average about eleven days. Of these cases thirteen died, and two of these with all the symptoms of acute yellow atrophy.

The evidence in favour of acute yellow atrophy being a rare form of malignant jaundice of obscure infective nature appears to us to outweigh that in favour of any other of the propositions.

The resemblance between the disease and phosphorus poisoning is important, in that it shews that certain poisons do possess the power of producing degeneration of the liver. But this resemblance is by no means so close as to justify the proposition that acute yellow atrophy is but an obscure form of phosphorus poisoning. On the contrary, there are important points of difference between the two conditions. In the first place, in jaundice due to phosphorus and other poisons, as well as in the forms of severe jaundice occurring in disease, the liver is enlarged and not atrophied. Experimentally also such an intense icterogenetic poison as tolulylenediamine was always found (W. Hunter) to produce in dogs marked swelling of the liver and the spleen, whereas atrophy of the liver constitutes the special feature of the disease before us.

Again, the percentage of fat in the liver of phosphorus poisoning is very greatly increased—some tenfold—from 3 to 30 per cent, and is due to a fatty infiltration, whilst in acute yellow atrophy the change is a necrobiotic one from the outset, and the quantity of fat, 4 to 5 per cent, is normal. Indeed, the observation that nearly every other degenerative change in the liver is accompanied by a fatty metamorphosis is sufficient to shew that the cause of acute yellow atrophy must differ essentially from the ordinary poisons (Wells).

On the other hand, the resemblances between acute yellow atrophy and the severest cases of malignant jaundice are even closer. Yet here again there are certain differences—notably the essentially destructive character of the liver change in acute yellow atrophy—which appear to indicate that the poison is not the same in both diseases. It can hardly be doubted, however, that it is of a similar character ; in both we have to do with a virulent organic poison, acting specially upon the liver. As to the nature of the infection, the extreme rarity of the disease indicates that it must be of altogether exceptional origin.

Nature of the Jaundice.—No obstruction is to be found in the larger bile-ducts ; and the jaundice was long regarded as an example of jaundice independent of obstruction, and was variously ascribed to suppression of liver function, to haematogenous origin of bile pigment, to paralysis of bile-ducts, and to spasm of bile-ducts. But bile pigments are not pre-formed in the blood ; and at the time the jaundice appears there is no evidence of suppression of biliary function. On the contrary, even to the very last, bile continues to be formed ; sometimes, indeed, there is

actual polycholia during the second stage, and in the majority of cases bile is to be found in the gall-bladder, sometimes in normal amount.

Although the larger bile-ducts are unobstructed, and usually contain only colourless mucus, the smaller ducts, on the contrary, are generally bile-stained and filled by degenerated epithelium. The condition presented is the same as that found after poisoning with toluylenediamine or phosphorus, the jaundice being due to catarrhal obstruction of the finest bile-ducts. This catarrh is probably toxæmic—that is, produced by the excretion in the bile of the injurious products which damage the liver-cells.

Symptoms.—At the onset there is nothing in the features of the malady to distinguish it from an ordinary attack of jaundice. The disease is ushered in with the same symptoms—loss of appetite, malaise, nausea and vomiting, and epigastric discomfort, followed in the course of a day or two by the appearance of jaundice. The only feature that may possibly mark it off from a simple attack of jaundice is the occurrence of some rise of temperature. This stage lasts on an average some five to six days; but it varies considerably. During this time the physical signs are in no sense obvious. The tongue is coated, the bowels constipated; the pulse averages 60-70 beats per minute, the respiration is unaffected; and, beyond perhaps some slight degree of epigastric tenderness on pressure, nothing abnormal is presented by the abdomen.

Suddenly a marked change occurs, ushered in usually by headache and severe and repeated vomiting. In a few hours the patient passes into a condition of drowsiness and semi-consciousness, followed by great restlessness and delirium, with dilated pupils. The patient may scream out, or attempt to get out of bed, or even become maniacal. Simultaneously the jaundice assumes a deeper and more greenish hue, the tongue becomes dry and brown, the pulse rapidly rises in frequency (120-140) and loses in strength, the respiration is quickened. The liver dulness is diminished and may be reduced to a finger's breadth, or even disappear. Leucine and tyrosine are found in the urine, and not infrequently albumin. The temperature, which in the first stage may have been considerably raised, now becomes subnormal. The vomiting, hitherto perhaps intermittent, recurs with greater severity than ever, and becomes almost continuous; the vomited matter frequently contains blood; blood may also be passed by the bowel, the constipated stools being dark and offensive; haemorrhages occur under the skin or from the nose and mouth, and in some cases there is a red rash; in women severe metrorrhagia sets in, and in pregnant women abortion or premature delivery ensues.

The second stage, marked by the above severe symptoms, is of short duration. Under the combination of them all the patient rapidly passes into a muttering delirium, with or without convulsions, and dies in from two to three days.

The jaundice is in the great majority of cases one of the earliest

symptoms, making its appearance a few days after the first feelings of illness. At first it differs in no respect from that due to simple catarrh, the urine giving the usual Gmelin's reaction for bile pigment. It may vary somewhat in intensity ; but, as a rule, it steadily increases till the second stage, when, with the onset of the nervous symptoms, it suddenly deepens and at the same time alters in character, the discoloration of the skin acquiring a greenish tint. With this change there may also be a change in the character of the pigments in the urine. The urine may still be dark and give a yellowish foam, as if from much bile pigment ; but, on testing, Gmelin's reaction may be faint or even entirely absent. In a few quite exceptional cases presenting all the other features of the disease, including atrophy of the liver, jaundice has been absent, or has been confined to the liver.

The diminution in the area of hepatic dulness usually does not become manifest until after the onset of the severe nervous symptoms, and often not till within a few hours of death. Within this period of time it proceeds so rapidly that in the course of forty-eight hours the vertical dulness in the right mammary line may be reduced from the normal 5 or 6 inches to 1 or $1\frac{1}{2}$ inch. The diminution first becomes manifest in the left lobe, and subsequently in the right, and is easily made out towards the end of life, all the more readily because of the absence of any abdominal distension. As subsequent examination shews, the diminished dulness is due partly to diminished volume, but also in part to a falling back of the flabby and greatly shrunken organ from the anterior abdominal wall. In a certain number of cases, however, in which earlier observations have been made, the stage of diminution is reported to have been preceded by one of enlargement. In one such case the hepatic dulness on the first examination was found normal : two days later it was increased ; and two days later still it was reduced below the normal size. The position in which the remaining dulness is to be detected is usually in the neighbourhood of the 6th rib, extending an interspace or a little more downwards.

In but few cases is the liver dulness normal, and they are usually cases in which the liver has been chronically enlarged, as by cirrhosis, fatty infiltration, gall-stones, or syphilis ; even in these, however, the dulness is reduced, although it does not fall below the normal.

As regards the frequency with which this change occurs, the records are unfortunately imperfect. Thus, out of 44 cases collected by one of us (W. H.), in only 24 is mention made of the condition of the liver during life. In 21 of these, shrinking was detected.

In some cases there is sensitiveness on pressure over the liver, sometimes to a very high degree, especially during the second stage. But this is not constant ; more usually there is merely dull pain over the epigastrium.

Gastro-intestinal Symptoms.—The gastric symptoms are prominent in all cases ; they include coated tongue, nausea, and above all vomiting. This is often met with in the first stage as one of the earliest symptoms ;

but it is a constant feature of the second stage, and is of a particularly urgent and severe character. The vomit soon tends to assume a dark colour from presence of altered blood, and resembles treacle in appearance ; sometimes it contains bile.

The bowels are usually constipated, and may be so throughout ; but in some cases, especially in the second stage, they are loose, and the motions very offensive. They often contain bile, and sometimes altered blood.

Fever.—A certain degree of fever is commonly met with in the first stage at the outset ; it then falls to normal or subnormal again, usually rising during the second stage. But there is no general rule.

Out of 16 cases, in 8 the temperature was subnormal or did not rise above 99° F.; in 3 it rose with the onset of nervous symptoms, attaining 105° to 106° F. just before death ; in 3 it was high (103°) to begin with, and fell to below normal in the second stage ; and in 2 it remained subnormal until the last twenty-four hours, when it rose to 105° F.

Haemorrhages are met with in more than one-half of the cases. Haematemesis is most common : melaena (one-fourth of the cases), petechiae, and ecchymoses under the skin, are not infrequent : less frequently epistaxis occurs, and in a few cases haematuria ; in women metrorrhagia is common.

The alkalinity of the blood has been found to be diminished (Kraus and v. Jaksch).

The Urine.—The urine is generally slightly diminished in quantity, varying in specific gravity from 1015 to 1030 ; it is deeply bile-stained, and sometimes throws down a heavy deposit of urates. It usually gives a well-marked reaction to Gmelin's test for *bile pigments*. But other pigments are obviously present ; for sometimes, notwithstanding bilious colour, this reaction is not given. It is probable that urobilin is greatly increased in such cases ; but on this point information is required. In one recent case indican was much increased. Bile acids have been demonstrated by certain observers ; but they are often present only in traces, and in some cases are entirely absent.

Albumin and casts are often present, but seldom in any quantity.

Sugar is not found.

The excretion of *nitrogen* has in some cases been much diminished, corresponding to the level of starvation, as might be expected, since little or no food is retained. In other cases, however, in spite of the small intake of nitrogen in the food, that in the urine has remained at the usual level, that is to say, nitrogen has been lost from the body ; the loss is not usually considerable, and, as far as the evidence goes at present, is no greater and is often less than that observed in many febrile conditions. Of special interest in acute yellow atrophy is the distribution of the nitrogen among the various substances in the urine which contain it.

The *urea* normally contains 80-90 per cent of the total nitrogen in the urine. In this disease the proportion is lower ; figures have been

found by German observers (49) varying from 52 to 81 per cent. Ewing and Wolf in 3 cases found 58 to 79 per cent.

The ammonia, which does not normally account for more than 5 per cent of the total nitrogen, has been found to contain from 12 to 20 per cent, and in one case (Münzer (49)) as much as 37 per cent. Ewing and Wolf found that the proportion becomes higher as the disease advances. The alteration between the ratios of urea and ammonia in the urine has suggested that the power of the liver to convert ammonia into urea is lost to a greater or less degree. Probable as this might appear, it is not a necessary conclusion from the data, for proportions of urea as low and of ammonia as high are found in healthy people who are supplying their nitrogenous needs from their own tissues, and in cases of severe vomiting the proportion of nitrogen in the urine in the form of ammonia has been found much higher.

The observation that in acute yellow atrophy as much as 79 per cent of the total nitrogen (7.2 grams) may be in the form of urea within two days of death (Ewing and Wolf) appears to shew that enough liver tissue is left to form this amount of urea ; unless it be interpreted as meaning that other tissues have a considerable urea-forming function.

Another explanation of the increase in the ammonia in the urine, and a probable one, is that ammonia is carried out of the body in combination with organic acids, and therefore cannot be turned into urea, as a consequence of which less urea is excreted. This is the explanation accepted in diabetes and many other instances of acid poisoning, and notably in cases of severe vomiting. Support is given to this view by the observations that the alkalinity of the blood is reduced in acute yellow atrophy, that selenocystic, diacetic, and other organic acids have been found in the urine of many cases, and that the administration of sodium bicarbonate has been found to be followed by a fall in the amount of ammonia in the urine.

The excretion of uric acid is normal or even raised. In the latter case the increase may be due to the passing out of uric acid derived from the disintegration of nuclein bodies in the liver. Weintraud's observation that the amount of uric acid in the urine was increased after feeding with thymus gland shews that the formation of uric acid from nuclein bodies can still go on.

A number of other nitrogenous substances, which may be regarded as derived from the autolysis of the liver proteins, are found in the urine. Of these the most important are leucine and tyrosine, which have for many years been recognised as a characteristic feature of the disease. Tyrosine is sometimes thrown down as crystals on cooling. Leucine appears on evaporation of the urine. Out of 34 cases collected by Thierfelder in which these bodies were looked for, they were both found in 17, and in 7 neither. Out of 23 cases collected by one of us (W. H.), both were found in 10, and neither in 9. These bodies are commonly present in the liver in the cases in which they do not appear in the urine ; this fact, and the occurrence of oxymandelic acid, which is probably derived from the desamidation of tyrosine, indicate that the power of splitting off the

amino group from amino bodies is not lost. Other autolytic products found in the urine are lactic, acetic, butyric, and succinic acids, and small quantities of albumoses and peptone.

It is interesting to note that amino acids are found in excess in the blood as well as in the liver and the urine. Indeed, Neuberg and Richter estimated that there was more tyrosine in the blood than could be accounted for by the hydrolysis of liver tissue, and suggested that the synthesis of amino acids from the intestine had failed. Another possibility is that these bodies are formed in the course of the cleavage of protein in the tissues, and are being carried to the liver, which is, however, unable to deal with them, and that therefore an accumulation takes place in the blood, and perhaps in the liver. The condition would then be analogous to that of the blood and liver as to fat in phosphorus poisoning.

Diagnosis.—The chief distinctive feature of the disease is jaundice, without evidence of obstruction of the large bile passages, running an acute course with severe mental symptoms and diminution of the liver dulness. The jaundice of portal pyaemia is usually less acute, and is accompanied by rigors, and by some focus of infection in the portal area, such as appendicitis or cholecystitis. In phosphorus poisoning severe vomiting occurs in the first stage, and there may be an interval of comparative health between the first and second stages; phosphorus may also be found in the vomit. In all these conditions the liver dulness is usually increased. From the sporadic and epidemic cases of icterus gravis the diagnosis is commonly impossible.

Prognosis.—Nearly all cases end fatally. The duration of the disease varies considerably. In the majority of cases it is not more than 14 days, and rarely does it exceed three weeks.

Duration of Disease.

THIERFELDER		HUNTER	
102 Cases		29 Cases	
Days.	Cases.	Days.	Cases.
2- 4	5	2- 4	4
5- 7	18	5- 7	3
8-14	31	8-14	8
15-21	22	15-21	5
3- 8 weeks	26	3- 8 weeks	9

The relative duration of the two stages of the disease varies within wide limits. In certain cases, in which the disease supervenes on some other morbid condition of liver, such as cirrhosis, it is not possible to determine when it commences.

First Stage.—In 24 cases in which information on this point is forthcoming, the duration of the first stage, from the onset of symptoms to the appearance of the nervous disturbances ushering in the second, varied from two days to three or four weeks. In two cases it exceeded four weeks; namely, over six weeks (Cayley), two months (Glynn).

Second Stage.—Of greater interest is it to ascertain the duration of the second stage, when the true nature of the disease is recognised.

Thus in 26 of W. Hunter's cases, in which information on that point is given, the duration of the second stage varied from one to seven days, and on an average was from two to three days. These results agree with those of Thierfelder, obtained from 118 cases.

The disease is not invariably fatal, for a considerable number of cases is recorded in which recovery has taken place. Dr. Wickham Legg in 1880 collected 28 cases of reputed recovery. Dr. Rolleston has recently recorded such a case; and several have been observed in which, after a more or less complete cessation of the disease, the remains of the changes of acute yellow atrophy have been subsequently found in the liver at an autopsy.

Treatment.—Cases are recorded in which recovery has followed the repeated transfusion of saline solution. Dr. Rolleston recommends dilute hydrocyanic acid, bimeconate of morphine, and effervescent mixtures for the vomiting; and salicylate of bismuth, β -naphthol, or minute doses of calomel to reduce any auto-intoxication from the intestine as far as possible. Milk should be the only food allowed, with free draughts of water, and some diuretic substance such as citrate of caffeine.

The high percentage of ammonia in the urine, and the fact that autolysis is favoured by an acid reaction of the tissues, suggest that the administration of sodium bicarbonate might be of value. If the vomiting renders it impossible to give it by the stomach, a 2 per cent solution might be given intravenously. If no food be retained enemas of a 5 or 10 per cent solution of dextrose may be given.

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JAUNDICE OF PHOSPHORUS POISONING

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THE jaundice of phosphorus poisoning is the best-known example of a jaundice produced by the action of drugs. It was formerly comparatively common; but since legislative measures have been taken in this country and Germany to enforce the use of the insoluble and non-poisonous form of the drug in the making of lucifer matches, it has become decidedly less frequent. In the years 1900, 1901, and 1902 there were 42 deaths in England and Wales caused by phosphorus out of 3495 from poisoning of all kinds (16). In 1906 there were 18 fatal cases of phosphorus poisoning, 9 men and 9 women; half of these were suicides (17). In Austria it is still very common. In the years 1893-98, for instance, 344 cases were admitted into the Allgemeine Krankenhaus at Prague alone, of which 235 were women (v. Jaksch). On the Continent it is taken to produce abortion; in 52 fatal cases at Graz in 1884-1900 86 per cent were in women of fruitful age. In 7 cases mentioned by Kratter in which phosphorus was used with that object, in only 2 was this effect produced, and both were fatal.

The poison is usually taken as an infusion of the heads of lucifer matches, sometimes in the form of those rat poisons which contain phosphorus. Six or seven match-heads containing yellow phosphorus, and even fewer, have been known to kill an infant.

Morbid Anatomy and Pathogeny.—The chief changes found post-VOL. IV.—PT. I

mortem are (i.) jaundice ; (ii.) haemorrhages ; usually small and punctiform, scattered over the various serous membranes—pleura, pericardium, mesentery, and in the mucous membrane of the stomach and intestine, under the skin and between the muscles ; sometimes of larger size, and met with in the liver, and in the cellular tissue of the abdomen or chest.

(iii.) *Degenerative Changes in the Liver, with Fatty Infiltration of the Liver and Heart.*—The liver is usually enlarged and presents the characters of a fatty liver—doughy to the feel, greasy on section, its lobules deeply bile-stained. In rare cases the liver may be diminished in size instead of increased. Its colour is commonly a uniform pale yellow ; but in some cases there are portions here and there of a more reddish-yellow colour, due to congestion of the centres of the lobules. On microscopic examination the outlines of the liver-cells are indistinct, the substance of the cell being converted into fine granular detritus, with large fat drops, especially in the outer zone of the lobule ; at a later stage the nucleus is affected by the poison and stains badly. The cells of the central zone often contain biliary pigment. The bile capillaries are obstructed by catarrhal products. The connective tissue throughout the liver is usually unaffected ; in a few cases it has been found in a state of proliferation.

On chemical examination a notable increase in fat is found. The normal liver contains about 3 per cent of fat, 76 per cent of water, and 21 per cent of non-fatty substance. In phosphorus poisoning the percentage of fat is as high as 30, water 60, and non-fatty tissue 10 per cent. A fat percentage of 37 has twice been recorded (Kraus and Sommer). This increase contrasts remarkably with acute yellow atrophy, in which the proportion of fat is normal. The examination of the melting-point of the fat obtained from the liver, and of its power of combining with iodine, shews that it is identical with the connective-tissue fat of the body. Further, in patients so wasted as to contain very little fat in the connective tissues its accumulation in the liver fails (Lebedeff) ; and the same has been shewn in animals (Rosenfeld). The fat in the liver, therefore, is not formed from the cell protein in that organ, but is brought there from other parts. This conclusion received further proof from Rosenfeld's observation that when a dog is fed upon a foreign fat, such as mutton fat, and afterwards poisoned by phosphorus, the fat in the liver is found to be of the same nature as that which was given as food (*vide Vol. I. p. 575*). The fault appears to be that the liver-cells have lost the power of utilising fat brought to them in the blood. The needs of the body not being satisfied, the fat depots are still stimulated to continue to discharge that material, which, therefore, accumulates, not only in the viscera, but in the blood. The heart and the pancreas also shew, though in a less degree, an increase in the fat content. In the kidney there is microscopically much fat to be seen, although analysis shews that the amount present is normal. In this case, and no doubt to some extent in the case of the liver, heart, and pancreas, the droplets represent fat which was previously present in the organ in a state of combination, but which has been set free at an early stage of

the tissue degradation, or autolysis, caused by phosphorus. Saxl has shewn that this occurs in the liver in the first stage of poisoning from the injection of phosphorus into the portal vein. The proportion of lecithin in the liver is diminished, whereas normally the greater part of the fat in the liver, as in the heart, is in this form. Glycogen disappears from the liver, probably owing to the oxidation of sugar, for there is no hyperglycaemia, and glycosuria is rare. Another suggestion is that the lactic acid sometimes found in the urine is derived from the vanished glycogen, complete oxidation having failed. The power of forming glycogen from ingested glucose appears, in animals, to be retained (Neubauer).

Chemical examination of the nitrogenous bodies in the liver shews that the total amount of nitrogen in the liver is diminished, and that a considerable degradation of protein tissue has taken place. The products are similar to, and in the main identical with, those found in the liver of acute yellow atrophy (see p. 120), in chloroform poisoning, and in the experimental autolysis of liver tissue, and for this reason their formation is ascribed to an ante-mortem autolysis of the liver. Jacoby found that the rate of autolysis in phosphorus poisoning was greater than normal, but was not increased by adding phosphorus to the viscus. Saxl, however, comes to an opposite conclusion in respect to the latter point. Wakeman found the proportion of the hexone bases, and especially of arginine, to be rather less in dogs than that resulting from the autolytic degeneration of the healthy viscus; there may be an over-action of the ferment arginase which breaks down that base. In the extremely rapid necrosis of the liver from another cause, however, namely, the action of haemagglutinative and haemolytic immune serums, Jackson and Pearce were unable to extract arginase, and the hexone bases were increased in quantity, although, as the total nitrogen was still more increased, the percentage of hexone nitrogen was less.

The kidneys are usually swollen and soft; the capsule strips easily; the cortex is increased in thickness, and pale, contrasting with the more purple colour of the medulla. On microscopic examination the epithelium of the convoluted tubules is swollen and fatty, or thrown off as casts. The heart is flabby; its muscle presents a more or less mottled appearance from fatty change, and is extremely friable. The spleen is usually enlarged, often to double its natural size, and full of blood; in other cases it is small and firm.

The blood contains an excess of fat. Its alkalinity and the volume of carbon dioxide that can be extracted from it are diminished. In the early days of the poisoning the number of red corpuscles is often above the normal, whilst that of the white cells varies. According to Silbermann, leucocytosis occurring in the first few days, with fever, is a sign of dangerous complications in the respiratory or digestive systems.

The stomach and intestines are inflamed in cases dying soon after taking the poison, and may be ulcerated.

Symptoms.—These vary considerably, according to the dose of the

poison taken and the rapidity of its absorption. Two stages may usually be distinguished : one in which the symptoms are mainly those of irritant poisoning, followed by a second in which more characteristic symptoms of toxic poisoning make their appearance, ushered in with jaundice. The duration of the first stage varies according to the amount of the poison taken. It usually lasts from some two to five days, but in exceptional cases may be fourteen to twenty-one days, and even longer.

The first symptoms usually begin a few hours after the poison has been taken, with severe burning pain in the epigastrium, intense nausea and vomiting. The vomiting continues almost incessantly, everything taken being rejected, till in the course of twenty-four hours or less the patient may be in a state of collapse. The respiration is very rapid, the pulse small and weak, the tongue and lips dry and red ; thirst is incessant. At this time there is great tenderness over the epigastrium and the region of the liver ; but the latter is not perceptibly enlarged. Death may occur in this stage in very severe cases ; but usually the irritant symptoms subside, and an apparent improvement in the condition of the patient takes place and continues for three or four days. In the second stage the patient becomes jaundiced. The vomiting returns with renewed severity, but the character of the vomit changes ; it now contains blood, dark or chocolate-coloured ; the pain and tenderness over the epigastrium and the region of the liver continue, the liver can be felt, and its dulness is increased. In some cases the spleen also is perceptibly enlarged. The abdomen becomes distended. Nervous symptoms appear—intense headache, sometimes hiccup ; drowsiness passing into coma, varied with attacks of delirium or convulsions ; and the patient rapidly sinks, dying either from exhaustion or, more suddenly, from heart failure, within twenty-four or forty-eight hours of the onset of the graver symptoms.

Jaundice is a very characteristic feature. In severe cases it is usually noticeable about the second or third day ; in milder cases not till the sixth or seventh day. It shews itself at first as a slight icteric tinge of conjunctiva, but is not fully manifested until the second stage of the disease is entered. Although a prominent symptom, it is by no means a constant one, nor is it necessarily proportionate to the severity of the poisoning. Hessler found it in 26 only out of 48 cases. On the other hand, it was absent in 1 only out of 10 cases recorded by Münzer, and that case was a mild one which ended in recovery. Even when present the jaundice may be slight throughout, although in most cases it is well pronounced.

The *temperature* is usually normal or subnormal throughout. It may be raised in the second stage to as much as 100° to 103° F. In rare cases it has risen as high as 107° F. just before death.

Haemorrhages are commonly present, but they are not so prominent in the jaundice of phosphorus poisoning as in other forms of severe jaundice, such as *icterus gravis* or acute yellow atrophy. At least this is true of haemorrhages under the skin. The most frequent situation

of the haemorrhage is the mucous membrane of the stomach, giving rise to black vomit. Although the occurrence of haemorrhage is not prominent clinically, it is a marked post-mortem feature of the disease.

The urine shews marked changes. Its quantity is usually more or less diminished, or it may be diminished at first, but afterwards increased, again to fall shortly before death, varying between $10\frac{1}{2}$ and 70 oz. (300 and 2000 c.c.). At no time is there anuria. Its specific gravity is from 1020 to 1037, according to quantity, its reaction strongly acid. The bile pigments and bile acids are nearly always present—the latter in very diminished quantity. Albumin is found, although not invariably, and usually in small quantity, and may be accompanied by fatty epithelial cells and fatty casts. In some cases blood is present. Sugar is a rare constituent; it was found by Walko in 6 out of 141 cases at Prague.

Total Nitrogen.—After the first two or three days the amount of nitrogen in the urine is increased, and remains at a level above that of starvation, although no food may be retained. The disintegration of protein tissue is therefore excessive.

Of this total amount of nitrogen the larger part continues throughout to be passed out in the form of urea. In health, urea constitutes from 85 to 90 per cent of the total nitrogen of the urine. In the first stage of the poisoning this proportion is unaltered. In the second it falls to 70 to 80 per cent.

Corresponding to this fall in the proportion of urea there is a rise in that of ammonia and, to a less extent, of other nitrogenous bodies. In health, from 4 to 6 per cent of the total nitrogen of the urine is excreted in the form of ammonia. In the second stage of phosphorus poisoning the percentage rises to 10 to 18.

Peptones are sometimes found in the urine; they were not present in any of Münzer's cases.

Leucine and *tyrosine* are sometimes present. Tyrosine was found in 7 out of 36 cases by Riess; in only 4 of these was it abundant. Leucine is less frequently found. The hexone base arginine and other amino bodies have been obtained from the urine. The power of depriving these substances of their amino groups is not lost, as is proved by the large amount of urea present, and the occurrence of such bodies as oxymandelic acid which is derived from the desamidation of tyrosine, but the further oxidation of which fails.

The amount of *uric acid* in the urine rises with the total nitrogen, but the relative proportions of the two are not materially affected.

Diacetic acid and *acetone* are frequently present in the urine as in other diseases in which the fat stores of the body are rapidly called upon. *Lactic acid* has also been found in many cases. Such organic acids are mainly excreted in combination with ammonia, and it is probable that the high proportion of ammonia acts beneficially by neutralising these acids which might otherwise still further diminish the alkalinity of the tissue fluids. If some other base, such as sodium bicarbonate, is given, the amount of ammonia in the urine falls.

Inorganic Constituents.—*Chlorides* fall to a low amount, and then gradually rise.

The amount of *phosphoric acid* in the urine is variable. Any increase, relative to the total nitrogen, may be due to the oxidation of some of the phosphorus taken, or to the liberation of phosphorus from lecithin, which contains it in greater proportion than other tissues. In favour of the latter view is the observation that the lecithin of the liver is diminished in quantity.

Sulphuric Acid.—The amount of this acid in phosphorus poisoning is variable. The *unoxidised or neutral sulphur* has been found to be increased by Starling and Hopkins and others.

The *ethereal sulphates* are sometimes increased. In one case the proportion to the inorganic sulphates was 1 to 5·9, instead of 1 to 10 as in health. On the other hand, they have been found diminished, for example, 1 to 20 (Starling and Hopkins), 1 to 54·6 (Münzer).

Nature of the Jaundice.—This problem is one of peculiar interest. Far more than any other form of jaundice, that of phosphorus poisoning was formerly held to establish the existence of a jaundice from suppression independent of obstruction. The data in favour of such a view are that the bile-ducts, or at least the larger bile-ducts, are free from obstruction, often indeed free from bile; the blood shews no evidence of any special destructive action, such as we meet with in the case of other icterogenetic poisons; and, lastly, the intense fatty change in the liver indicates that the poison acts specially on the liver-cell.

Nevertheless, the formation of a fair amount of urea throughout shews that the liver is still active, and in the first stage of the poisoning Stadelmann found the excretion of bile to be increased. Further, the cutting of the liver out of the circulation does not in animals lead to jaundice, the activity of the liver being essential for the formation of biliary pigment. The functions of the liver, therefore, although they are doubtless injuriously affected, are not suppressed. On the other hand, the small bile-ducts, or many of them, are blocked with disintegrated cells and mucus, and this is sufficient to explain both the jaundice and the emptiness of the larger ducts.

Changes in those ducts have long been noted and described. Thus, Oscar Wyss (1867), in experiments on dogs, found the larger ducts free from bile and unstained, whilst the smaller ones were filled with thick mucus which prevented the flow of the bile downwards. And similar appearances have been noted in man (Ebstein, Eppinger).

To sum up, then: the jaundice of phosphorus poisoning is due to obstruction in the smaller bile passages set up by changes in their epithelium and secretion.

Diagnosis.—This must rest in the main upon the history or likelihood of the ingestion of the poison, or its discovery in the vomit. In early stages a garlic-like odour may often be detected in the breath. If the vomit be heated in a flask in complete darkness, faintly luminous vapours may be perceived, possessing the characteristic odour. Further methods

for testing fluids for phosphorus will be found in text-books on toxicology.

In the second stage phosphorus is not likely to be found in the rejected matters, and the clinical appearances are difficult to distinguish from those of acute yellow atrophy, under which heading (see p. 122) the distinctions between the two conditions are discussed.

The prognosis in severe cases is serious. The mortality in 344 cases taken into hospital in Prague was 33 per cent.

Treatment.—In the early stage the stomach should be washed out. Oxidising agents should then be given to hasten the transformation of the phosphorus into its harmless oxidised forms. For this purpose copious draughts of 5 to 1 per cent potassium permanganate are recommended. Old oil of turpentine is also given, in doses of 40 minims, emulsified with mucilage, every quarter of an hour for four doses, and then every six or eight hours, and many severe cases have recovered with its use. The addition of peroxide of hydrogen or of sanitas (containing peroxide of hydrogen, camphoric acid, and turpentine) to the old oil of turpentine has been suggested as likely to hasten the oxidation of the phosphorus. When vomiting is severe, rectal injections of a 5 or 10 per cent solution of dextrose may be given.

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DELAYED CHLOROFORM POISONING

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SINCE this condition has attracted considerable attention, and since the liver shews very definite changes, it is advisable to include a description of it among the diseases of that organ. Attention was first directed to "delayed chloroform poisoning" by Dr. Leonard Guthrie in 1894, in a report of nine cases in which death occurred within from ten hours to six days of operations performed under chloroform. The exact numbers of hours which elapsed between the operations and the deaths of the patients were 10, 12, 13, 16, 24, 27, 30, 53, and 150 respectively. In a tenth case recovery took place after symptoms of great gravity had lasted nearly three days. The conclusions he drew as to the cause of death were :—(1) that the death was due to auto-intoxication from inadequacy of the liver; (2) that a fatty condition of the liver with functional disturbance existed before the operation; (3) that chloroform and shock combined aggravated this fatty condition. These conclusions did not meet with acceptance, the fatalities being considered to be due to carbolic acid poisoning or to pulmonary embolism. In a second series of four fatal cases, three of them in children, published in 1903, he was able to exclude carbolic acid and fat embolism as the cause of death. Since then there have been numerous communications on this subject; in 1904 Mr. Stiles and Dr. MacDonald gave details of several fatal cases and of experiments on animals, and Brackett, Stone, and Low recorded fatal cases following ether anaesthesia, with symptoms and changes similar to those previously attributed to the effects of chloroform, and described for the first time the existence of severe fatty acid intoxication. In 1906 Telford and Falconer shewed that a similar condition of diaceturia may follow ethyl-chloride narcosis. The whole state of our knowledge regarding the symptoms and probable nature of these cases was summarised in 1907 by Dr. Guthrie.

Morbid Anatomy.—The most constant changes are presented by the liver, which is strikingly pale, sometimes of a bright canary colour, sometimes fawn-coloured, studded and streaked with minute purple specks and lines. It may be large, normal, or reduced in size. It is intensely fatty, its cells distended with fat globules of varying size, sometimes most evident in the central and sometimes in the peripheral part of the lobules. The nuclei of the cells usually, but not always, stain well with haematoxylin. The nuclei of the capillaries are well stained and prominent. In some cases a small-celled infiltration has been found around the bile-ducts. Dr. Guthrie states that the changes in the liver did not resemble acute yellow atrophy in any of his cases, but were those of fatty infiltration, with sometimes slight granular degeneration of the

hepatic cells. On the other hand, in some of the cases recorded by Schenk and Ballin the post-mortem appearances are described as those of acute yellow atrophy, and in others as fatty degeneration or infiltration of the liver. These cases had in common that one or two days after an operation slight jaundice appeared, which was followed by vomiting, violent delirium, coma and death in all but one, and that the patients were all adults, and except in one case the operations were upon the abdomen. Fatty changes were found either in the liver, heart, kidneys, or in all these organs.

The *heart* may shew no abnormality, but occasionally it is fatty, and the muscular striae granular and indistinct. Fatty change in the liver and heart was noticed by Sabarth in 1866 (quoted by Nothnagel) in nine cases of death from chloroform.

The *kidneys* often shew pronounced granular degeneration with widespread fatty change in the tubules, the globules being situated for the most part towards the bases of the cells.

The *lungs* shew no characteristic changes. The *gastric mucosa* may present minute haemorrhages, but in other cases shews nothing abnormal.

Pathogenesis.—These pathological changes correspond with those that can be produced experimentally by chloroform and ether, as was shewn by Nothnagel in 1866, and later by Thiem and Fischer, Ostertag, and Rosenfeld. Nothnagel compared sections of the liver removed before and after anaesthesia produced by putting chloroform into the stomach of a rabbit, and found that microscopically whilst the former shewed the usual fat droplets, in the latter the droplets were seen throughout the cells. The fatty change was least after inhalation of ether, and most severe when ether or chloroform was placed in the stomach.

Mr. Stiles and Dr. MacDonald have recently obtained similar results after chloroform inhalation, and in a slighter degree after ether. Wakeman has found that the protein of the liver-cells undergoes a cleavage in animals similar to that taking place in phosphorus poisoning and in autolysis of the liver. Since the first change observed in autolysis is one which renders the normal fatty content of organs visible, it is probable that this accounts for some of the fatty change described in man. Thus, Rubow found that in chloroform poisoning both hearts and kidneys which shewed under the microscope extensive fatty metamorphosis contained only a normal proportion of fat.

Brackett, Stone, and Low have shewn that the symptoms of the cyclical vomiting of children accompanied by acetonuria are practically the same as those of a minor degree of post-anaesthetic poisoning. In the few cases of fatal cyclical vomiting in which an autopsy has been obtained, the liver, kidneys, and other organs have also shewn fatty changes precisely similar to those met with in cases of delayed anaesthetic poisoning (Griffith, Langmead).

On the strength of these similarities, Dr. Guthrie emphasises this fatty change in the liver, and the acid intoxication which accompanies it,

as the determining factors responsible for the symptom-group of delayed chloroform poisoning. The conditions in which it is likely to be met with are such as are known to be associated with fatty liver, e.g. cases of acute and chronic suppuration, and of rickets and infantile paralysis which have been treated by over-fattening and insufficient exercise; probably, also, conditions such as alcoholism, and certainly starvation and cyclical vomiting with acetonuria. The fattening diet often given in rickets is probably not an essential factor, for Telford has described cases in rickety children who had neither been fed on such a diet nor treated by cod-liver oil. In favour of the view that disturbance in fat metabolism plays some part in the pathogeny of this condition is the frequency of acetonuria after anaesthesia. Becker found acetonuria or diaceturia in 67 per cent of 251 cases, especially in children, and Dr. Hill Abram in 64 per cent of his cases.

To connect post-anaesthetic poisoning exclusively with disturbances in fat metabolism is, in my opinion, to exaggerate the importance of this change, and to underestimate the importance of the glycogenetic and proteolytic functional liver disturbances of which it is the result. Disturbances in fat metabolism are largely connected in the first instance with deficiency of carbohydrate material in the food and of glycogen in the cell; and in the second instance with increased tissue proteolysis. The functionally active cell possesses such an urgent need for carbohydrate that it attempts to meet this need in all circumstances. If it cannot get it from sugar, it takes it from tissue protein; if both fail it takes it from fats. The excessive fat metabolism thus necessitated includes: (1) a transference of fat in increased quantity from its peripheral depots to the liver in the first instance; (2) a liberation of the fat already present, bound up with the nucleo-protein element of its tissue; and (3) an increased acidosis (with acetonuria) consequent on insufficient oxidation of the fat. This increased acidosis does not necessarily of itself cause any special disturbance. It is always significant, however, of (a) deficiency of carbohydrate food, and (b) excessive tissue proteolysis consequent on want of sufficient food protein and on toxic action. It may indeed, under certain conditions, become a factor in causing additional functional and even structural disturbance, viz. by further lowering the intracellular alkalinity of the liver-cell already depressed by pre-existing conditions of disease, inanition, recurrent vomiting, and influence of infective disease. But even in these circumstances the essential factors responsible for the increased fat metabolism (with its acetonuria) are: (1) the want of carbohydrate and protein material responsible for the increased fat metabolism; and (2) the increased tissue proteolysis which is the result of this deficiency. Amongst such factors must also be reckoned all those of toxic nature which depress the functions of the liver. Among these, chloroform must be considered as one of the most potent. This is shewn by the degree of fat changes and acetonuria which follow its administration, both clinically and experimentally. Under certain conditions—fortunately rare in combination—the toxic action of chloroform may injure the liver-cell to the point at which its

functions are almost in abeyance. The most vital of these are the anti-toxic functions it discharges in relation to the portal blood; and it is the depression, followed later by the suppression of these functions, that give rise to the toxic cerebral symptoms characteristic of the condition. The condition is thus essentially a toxæmia of hepatic origin due to the poisonous action of chloroform on the liver-cell, already depressed in its functional activity by pre-existing causes involving deficiency of carbohydrate food material and by excessive tissue proteolysis. The fat changes are at once the expression of this deficiency and the measure of the degree of strain placed upon the cell in maintaining its energy. They therefore affect those organs, the vital functions of which must continue to be active, however depressed by the influence of the chloroform, namely, the liver, in respect of the vital antitoxic functions it performs in relation to the poisonous portal blood, the heart in relation to circulation, and the kidney in relation to excretion. They affect the liver in highest degree, since its functional activities are not only the most numerous and complex of any organ, but include fat metabolism as one of their chief.

Symptoms.—*Vomiting* is perhaps the earliest and most characteristic symptom. It appears at first to be the usual sickness after anaesthesia; but instead of subsiding after twelve hours or so, it continues, becomes more frequent and persistent, and soon the vomit becomes coffee-ground and black from the presence of blood. Nothing is retained, and the *thirst* is intense. The general symptoms accompanying this condition are of a cerebral character—at first great restlessness, with dilated or unequal pupils, flushed face, and anxious and terrified expression, followed suddenly by wild excitement, tossing and struggling, grinding of teeth, wild piercing shrieks, and maniacal delirium passing soon into drowsiness and coma, which deepens till death occurs, the average duration of symptoms from first to last being three or four days. Jaundice is rare; it was not observed in any of Dr. Guthrie's cases. The symptoms in miniature are not uncommon in a large proportion of cases after operations under anaesthetics, but usually pass off. Although the number of fatal cases already recorded approaches one hundred, it is probable, as Dr. Guthrie points out, that this number by no means represents the whole; and that many such cases have hitherto been ascribed to shock, fat-embolism, and other conditions. The *pulse* is quickened from the first, and becomes very rapid, weak, and almost uncountable with the onset of the nervous symptoms. The *temperature* is not affected at first, but may rise to 101-102° and 105° or 106° F. before death. The *wine* almost invariably contains acetone and diacetic acid, and the smell of acetone becomes noticeable in the breath. The symptoms thus resemble those of toxæmia, so commonly seen in cases of severe liver disease, such as cirrhosis, and, even more closely, those of acute yellow atrophy.

Treatment.—*Dietetic.*—The chief indication is to prevent the liver being deprived of the proper amount of food immediately before chloroform anaesthesia. This indication is specially urgent when, from existing

disease, vomiting, or diarrhoea, the liver is already functionally depressed from want of food. The further privation of food preparatory to chloroform anaesthesia, which would be immaterial in a healthy person, may then become an important factor. The effect of the chloroform falls on a liver probably already fatty and functionally depressed by want of food, toxic influences, and often by mental emotion; delayed chloroform poisoning may in consequence be induced even by doses usually well borne. The necessity then for fuller feeding of patients prior to administration of chloroform is all the more urgent, inasmuch as food has necessarily in many cases to be withheld for some time after the operation. Hence the great majority of recorded cases have been in patients requiring abdominal operations. The withholding of food in preparation for the operation has probably erred on the side of excess, or has at least been aggravated by the condition of malnutrition and asthenia accompanying the disease itself.

Fatty infiltration of the liver in animals poisoned with phosphorus or chloroform, or in simple inanition, can be prevented by the supply of protein and carbohydrate food. (Gading (26), Ostertag.)

The measures which suggest themselves in this relation include, therefore, special precautions in the way of feeding patients (ill-nourished or the subject of vomiting) for twenty-four or forty-eight hours prior to any operation and up to within a few hours of the operation, and by nutrient enemas immediately after operation. An important element of the food—whether administered by the mouth or by the rectum—should be sugar, as at once the most easily assimilated and the most readily available for purposes of energy production.¹ But protein food (peptonised) is also important, since, apart from the nutritive properties of protein, the ammonia formed from it and absorbed into the portal blood plays an important part in controlling the autolytic activities in the liver-cell and in neutralising the fatty acids formed in excess.

Medicinal.—The need for alkalis in some form or other seems indeed to be urgent, both before the operation in cases of asthenia, and afterwards. It may be given in the form of saline enemas in the strength of 2 drams of bicarbonate of sodium to the pint; or subcutaneously, or in the form of citrate of sodium in milk, as reported by Dr. Wilson. When the symptoms have set in or are threatened from persistent vomiting, the patient should be induced to drink as freely as possible. If the fluid be returned, as it sometimes is, large saline enemas should be given, or the stomach be washed out with saline containing 2 to 3 drams of bicarbonate of sodium. No relief is afforded by administration of bismuth or opiates; the latter indeed are probably harmful. To maintain the heart's action, strychnine, caffeine, and administration of oxygen may be tried.

¹ Since this article was written, both Dr. Beddard and Dr. Bainbridge have advocated the administration of sugar in these cases when the symptoms have set in. Dr. Beddard suggests intravenous infusion of 6 per cent dextrose. Dr. Bainbridge quotes Waldvogel's observation that patients who took carbohydrate freely before and after operation seemed less liable to acetonuria.

But the most effective measure is to relieve the patient of some of his toxic blood by venesection and subsequent infusion of normal saline solution.

In one of the most striking and severe cases recorded, that by Ballin, in which the symptoms followed appendectomy and resembled acute yellow atrophy, the recovery dated from the time when venesection and infusion were carried out. The patient fell into a profuse perspiration and made a good recovery.

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DISEASES OF THE BLOOD-VESSELS OF THE LIVER

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PYLEPHLEBITIS.—**Definition.**—Inflammation of the wall of the portal vein, or of its branches, leading to thrombosis (pylethrombosis, adhesive pylephlebitis), or to suppuration (suppurative pylephlebitis, portal pyaemia).

Pathology.—In this, as in all other conditions in which both the blood and the vessels are diseased, opinion has ascribed the chief part first to the one and then to the other of the two. It is, however, now

generally believed that the vessel wall is always affected, whether the source of the disease lie in the blood or no. It seems best, therefore, to adopt a nomenclature on this basis. On the other hand, it is also allowed that, with few exceptions, the phlebitis arises from infection or from morbid bodies in the blood. But the cases differ widely. In some the virus is weak, in others very active. In the former the forces of defence have time and strength to throw up barricades, and an adhesive inflammation is produced. In the latter all resistance is overwhelmed, intravascular suppuration results, and the poison then spreads itself by the vessels into the furthest parts of the liver, and even into the general system. Therefore, although the difference between the two is in the great majority of cases a difference merely of degree, yet, since the clinical symptoms differ much, and since, also, in some cases the cause differs in kind, a separate description of each class will be given.

THROMBOSIS OF THE PORTAL VEIN (PYLEPHLEBITIS ADHAESIVA, PYLETHROMBOSIS).—**Pathology.**—Thrombosis of the portal vein may occur under several conditions. The cause may be chronic disease of the vein ; Welch has referred to several cases of calcification of the coats of the vessel, Borrmann has described phlebosclerosis, and syphilitic endophlebitis has been mentioned (Rolleston). Or the vein or some of its intrahepatic branches may be attacked by inflammation extending from neighbouring tissues ; thus, portal thrombosis may be caused by abscesses in or near the liver, by cholecystitis or cholangitis, or by inflammation of the pancreas or of the structures near it. Cirrhosis of the liver is often alleged as a cause of thrombosis, and as an instance of inflammation beginning outside the vein. It was present in 22 out of Dr. Rolleston's 60 collected cases, but, as both he and Dr. Langdon Brown point out, it is rather a disposing than an exciting cause. It has been recorded as due to adhesive tuberculous peritonitis (F. Taylor). Frerichs mentions an instance in which the cause was apparently local peritonitis caused by a blow on the epigastrium. The patient, a man of forty-six, had twice been struck there, the first time eleven years and the second eighteen weeks before death. On each occasion he had severe abdominal pain and epigastric swelling. At the autopsy there was found both old and recent inflammation in the upper part of the peritoneum. If Frerichs' patient had not received a second injury, his case would have resembled that of the patient mentioned by Welch, in whom Delafield diagnosed traumatic portal thrombosis. Again, the vein may be constricted by new growth, malignant or syphilitic, so that the circulation is retarded or stopped. Such a condition is very favourable to thrombosis, which then probably depends upon microbic infection as its immediate or exciting cause. Or it may be actually invaded by cancer, or by gumma, or by one of the nodules of hepatic hyperplasia which are seen in some cases of cirrhosis, and are called multiple adenoma (Turner, Delépine, Powell (11)). In a second group of cases the thrombosis begins in a tributary and extends to the portal vein. Splenic

disease, for instance, such as infarction, abscess, or perisplenitis, may set up thrombosis, which begins in the splenic vein and extends into the portal trunk. Two cases dependent on gastric ulcer are mentioned by Dr. Wickham Legg. Strangulation of the intestine may cause thrombosis of the mesenteric vein (Newton Pitt). Or appendicitis or intestinal ulceration may have the same effect. The latter, however, are more likely to cause suppurative than adhesive phlebitis.

In all these cases the disease is the result of local conditions, but it may also be produced by general diseases. Marasmus, which is an occasional cause, was originally supposed to act merely by delaying the blood flow. But, as Welch has pointed out, it has been repeatedly proved in recent years that marantic thrombosis is due to bacteria. Fagge recorded a case following child-birth and associated with phlegmasia alba, and, according to Schmorl (14), puerperal eclampsia may produce it. Dr. Rolleston mentions two cases in which portal thrombosis, for which no cause could be found, was associated with thrombosis elsewhere. All this group may be ascribed with probability to general infection. To sum up, it may therefore be stated that the great majority of the cases depend upon local conditions; that, whether of local or general origin, infection is the most probable cause in all but those in which the vein is invaded by new growth, or by multiple adenoma, and is not excluded even in these; and that in a few cases no explanation can be given.

Morbid Anatomy.—When thrombosis has occurred shortly before death the vein is found distended with the clot, and both it and its branches of origin may be dilated on the distal side. The wall of the vein is in some cases sclerosed or calcified. Microscopically, its internal surface shews the usual appearance of endophlebitis. The clot in the most recent cases is deep red, and at any rate slightly adherent to the walls. If a little time elapse before death, it becomes partly decolorised, firmer, and more granular. Sometimes it is soft in the middle and firmer in the outer part. This may be due to a necrosis of bacterial origin, which if continued would canalise the clot and lead to suppurative inflammation. In thrombosis of old standing the appearances are different. In one example, related by Dr. Langdon Brown, portal thrombosis had been diagnosed by Jenner twenty years before death. "There was extreme varicosity of veins in the portal fissure and foramen of Winslow. The portal vein could nowhere be found, until dissecting deep into the portal fissure there were found two tough, narrow fibrous bands, one running right, one left, and uniting in what was probably the portal vein; a minute channel in the middle of each fibrous band, coming to an end as soon as the liver was entered. Liver natural, except pale. Tracing branches of portal vein within liver towards portal fissure, they came to a complete end just at the fissure and hard upon the fibrous bands spoken of. Hepatic veins natural. Gall-bladder and ducts natural. No splenic vein could be found."

The spleen is generally enlarged from engorgement, and the intestines

may, when the superior mesenteric vein is affected, be almost gangrenous. The part which feels the effect most is the jejunum, as it has no anastomosis with parietal veins. Dr. Rolleston has seen secondary ulceration in the stomach.

The *liver* is likely to be cirrhotic since cirrhosis is a frequent antecedent. But there appears to be little evidence that cirrhosis is produced by portal thrombosis. Infarcts have sometimes been found, and sometimes fatty change, or atrophy of the liver cells. In Dr. Langdon Brown's case of twenty years' standing the liver, though pale, was natural.

Symptoms.—In a large proportion of cases there is some pre-existing abdominal disease. Out of 41 cases collected by Dr. Langdon Brown there were 15 cases of cirrhosis, 7 of malignant disease of the liver, stomach, or pancreas, and 4 of suppurative disease connected with the intestines. In such cases the addition of portal thrombosis may be wholly latent and add nothing fresh to the clinical picture. But more commonly after a period of long illness ascites rapidly appears, the spleen enlarges, there is haematemesis, the stools are loose and often mixed with blood, the urine becomes very scanty, and the patient gradually sinks from exhaustion, or possibly from collapse after severe haematemesis. Sometimes severe and repeated haematemesis precedes all other symptoms and leads rapidly to death. Occasionally there is great enlargement of the superficial abdominal veins. Occasionally, especially when the superior mesenteric vein is greatly affected, the attack is ushered in by severe abdominal pain, and simulates acute intestinal obstruction.

If there is severe haematemesis or diarrhoea the spleen is less likely to enlarge, and ascites may prevent the spleen from being felt. Alimentary glycosuria has been stated to be diagnostic of portal thrombosis, but is quite exceptional.

Diagnosis.—This is seldom made during life. Ascites, haematemesis, and enlargement of the spleen are ordinary symptoms of uncomplicated cirrhosis of the liver. Unless a sudden abdominal pain or the passage of bloody stools occurs, it is not likely that the thrombosis will even be suspected. It can hardly ever be more than a matter of conjecture, and it might almost be said that it is wise never to diagnose it at all.

Prognosis.—The condition usually leads to death. Dr. Langdon Brown found that cases with cirrhosis lasted from two to twenty-six months, cases with malignant disease from eleven weeks to four months and a half, and cases due to peritoneal adhesions a still longer time. On the other hand, out of 34 cases, 7 died in less than a week and 7 others in less than a month. That recovery is possible is proved by cases reported by Lyons, Osler, and Rogers, and by Jenner's case quoted above. Lyons' patient suffered with ascites from May 1870 till December 1871, and was tapped thirty-five times; after this she enjoyed six years of tolerable health, and died in consequence of a fractured rib. Jenner's patient had recurrent haematemesis at intervals of about ten months for twenty years, and died of it. Where diagnosis is so uncertain, no case of recovery can be admitted which is not proved by subsequent dissection.

Treatment.—The treatment of ascites and haematemesis does not differ from that proper in cases of cirrhosis of the liver. Where bloody stools and symptoms like those of abdominal obstruction exist, it is not improbable that an operation will be attempted. No operative treatment, however, is useful. The establishment of an anastomotic circulation is the only procedure that could relieve the condition. But the patient is too ill, and the handling of the tissues is likely to lead to an extension rather than to a cure of the process.

On experimental grounds, the use of citric acid, or potassium citrate in 30-grain doses, has been recommended to prevent the further formation of clots. But, as Dr. Rolleston points out, there is some risk in this treatment. In some cases of cirrhosis the alkalinity and coagulating power of the blood are diminished. These could not be benefited, and might probably be harmed by the citric acid treatment. Unfortunately the methods of measuring these qualities, which are available for clinical purposes, are open to criticism.

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SUPPURATIVE PYLEPHLEBITIS (PORTAL PYAEMIA. MULTIPLE ABSCESS OF THE LIVER).—**Pathology.**—The condition is due to an infection, the source of which is sometimes obscure, but in most cases is clearly traceable to an original lesion within the area of the portal system. It sometimes happens that in general pyaemia infection is carried by the hepatic artery. But this form, to which the term pyaemic abscess is sometimes restricted, is only of pathological interest, and need not be further considered.

The original lesion of suppurative pylephlebitis, and of multiple abscess of portal origin, is always a breach of surface somewhere in the intestinal canal or a focus of suppuration in the area from which the portal vein arises, in the neighbourhood of the vein itself, or in the liver. But it is remarkable how much more commonly infection arises from some parts than from others. Dr. Langdon Brown (2) in two publications on the subject has collected 72 cases; the original focus was in the vermiform appendix and caecum in 29, in the stomach in 6, rectum 6, rest of intestines 6, local peritoneal or subperitoneal abscess 5, umbilicus (infantile) 2, spleen 1, bristle in mesenteric vein 1, gall-stones 6, a

suppurating ovary 1, and was not traced in 9 cases. The original lesion is practically always some form of ulceration. Occasionally foreign bodies, such as a fish bone (Lambron, Winge), a bristle (S. Phillips), an iron filing (Semmola and Goffredi), have been found in the portal vein or in one of its branches, but their presence implies a breach of surface in the intestine. Though there are many forms of ulceration in the alimentary canal, it is only one or two that give rise to pylephlebitis. Enteric fever is an extremely common cause of intestinal ulcers in England, but it hardly ever infects the portal vein, though it is a frequent cause of cholecystitis. Tuberculous ulceration has never been recorded as a cause. Dysenteric ulceration is very common in India, and a good many cases are seen here on their return, but it is the rarest possible thing for pylephlebitis to ensue. The single or tropical abscess due to the *Entamoeba histolytica* is a recognised sequel, but there is some reason to believe that in these cases the infection does not pass by the vein, but migrates across the peritoneum. Gastric ulcers are very common, but none of the cases in Dr. Langdon Brown's list were uncomplicated, all shewing some suppuration in the peritoneum or other parts which may have been the source of infection. In one case the ulcer had become adherent to the liver, and had formed an abscess of which the wall was partly formed by denuded hepatic tissue (Carrington). This is rather an infection through the branches of distribution within the liver, than through those of origin. Dr. Langdon Brown suggests that infection does not easily occur from an open ulcer which has free communication with the surface of the canal, but only in cases in which the products of ulceration are in some way pent up, or under pressure. This hypothesis explains the relative frequency with which appendix cases and the various forms of subperitoneal abscess figure in the list of causes. It must, however, be understood that "frequency" is only comparative; suppurative pylephlebitis is a very rare sequel to any disease, and even in appendicitis, its most frequent antecedent, its incidence is probably not more than 0·5 per cent of all cases (Treves (10)).

The path of infection is through the small veins near the original lesion. Sometimes a thrombus is found in one of these, sometimes in one of the main tributaries of the portal vein. But often the portal vein is the first to be attacked, and often again the virus passes right through the portal system and stops only in the capillaries of the liver. Then multiple hepatic abscess results without any traceable pylephlebitis. But the process is the same, and it is, after all, a difference in degree alone. The venules from which the capillaries arise are probably inflamed in all such cases. Occasionally gall-stones produce ulcers in the gall-bladder or one of the ducts, which extend into the portal vein or one of its branches. The infection is not always confined to the portal vein or liver; it is sometimes carried into the vena cava (in 16 cases out of the 72 in Dr. Langdon Brown's collection), and produces secondary abscesses elsewhere. As might be expected, the lungs, the next capillary system, are the usual site for such metastases. Empyema, however, is probably

due to direct lymphatic infection. In a few cases the infection goes through to the left heart, and gives rise to cerebral abscess, and to infarcts in the brain, heart, and kidneys.

The infective agent varies; *B. coli* appears to have been the most often recognised, but diplococci, staphylococci, and streptococci have also been found, as well as other species which were not identified. In one case the pus was sterile (Rolleston).

Morbid Anatomy.—The vein itself generally contains a fluid mass of sanguous pus. It is sometimes distended so as to form an abscess of considerable size, lying partly inside and partly outside the liver. Rupture of the vein has once been recorded. The coats of the vein are thickened and swollen. The collection of pus is often bounded at either end by a solid clot. Sometimes there are several such clots in the vein and its branches, forming a discontinuous thrombus without any affection of the vein in the intervals. It is not uncommon to see a solid clot blocking the mouth of the splenic or a mesenteric vein, and thus preventing the spread of infection in that direction. In the great majority of cases the infection travels with the blood, but retrograde infection, against the current, is acknowledged to occur.

Beyond the suppurative area in the portal vein, or without any such area existing, many small abscesses are often visible in the liver. The infected particles come either from the portal thrombus, or direct from the original focus. Sometimes there are a few large abscesses formed by the coalescence of many smaller. The liver is usually large and congested. There is often suppuration in the peritoneum near the transverse fissure of the liver; sometimes there is general peritonitis. Sometimes, as a consequence of thrombosis of the mesenteric vein, the intestines are congested, but the obstruction caused by the portal vein is not so great as in the adhesive form. The spleen is generally enlarged either from a thrombus blocking the splenic vein, or from the effect of the disease on the blood. As a rule there is also evidence of appendicitis, or of some lesion in the intestinal canal, or of a circumscribed abscess behind, occasionally within, the peritoneum. Sometimes an empyema exists, usually upon the right side, occasionally metastatic abscesses are found in the lungs or brain, or there is evidence of infective endocarditis.

Symptoms, Course, and Progress.—The symptoms may be divided into two groups; the first consists of those common to all forms of pyaemia, the second of those indicating disease of the liver. (1) Symptoms of pyaemia. Fever is high and irregular with wide extremes. Rigors are frequent, and there are often profuse sweats. The pulse is very rapid, and the respiration also. The tongue is dry. The patient becomes rapidly prostrated. (2) The local symptoms are at first rather abdominal than hepatic, and consist of pain, nausea, vomiting, diarrhoea, and distension of the abdomen. But usually after a little while the liver becomes enlarged and tender, slight jaundice often appears, and the spleen sometimes becomes palpable. The onset of these symptoms may be masked by the original disease, for instance, by those of appendicitis

or of gall-stones, but Dr. Langdon Brown found that in his series an acute onset was almost twice as common as a gradual.

Ascites and enlargement of the superficial veins are less often seen in this disease than in pylethrombosis. The urine is scanty and high-coloured ; it sometimes contains albumin ; pus is noted once by Dr. Langdon Brown.

The disease runs its course in about seven weeks, it rarely lasts longer and is often shorter. The patient becomes delirious and dies in a state of coma.

Prognosis.—Although the disease is almost always fatal there is evidence, as Dr. Langdon Brown points out, that recovery may exceptionally occur. He cites the following cases. Lawson, consulting surgeon to the Seamen's Hospital, had suffered from some disease of the liver when in India. He died of granular kidney ten years after his return to England. The liver contained scars of white cartilaginous substance and small abscesses (Budd). A girl, aged 18, died of lardaceous disease from an old pelvic abscess, probably due to appendicitis. The portal vein was occluded, its walls thickened, and it contained pus stained with bile. In various parts of the liver there were small scars with caseous centres, and in one place there was a distinct mass of caseous matter which was probably the remains of an abscess (Goodhart). A boy, aged 11, had multiple abscesses of the liver, with high fever and severe illness. There was no jaundice, and no cause was found. After many abscesses had been drained with a trocar a free incision was made and the patient recovered (S. West). A girl, aged 15, after a third attack of appendicitis shewed symptoms of portal pyaemia. Laparotomy was performed, and the liver, which was considerably enlarged, was found to be very soft and to be covered with yellow foci the size of pin-pricks. There was no evidence of tuberculosis. She recovered (Treves (11)). A boy, aged 10, had a pyaemic abscess of the liver due to appendicitis. The appendix was removed and the liver abscess drained ; the boy recovered (Morton). It will be noticed, however, that in only one of these cases was the vein itself seen to be affected. It is reasonable to suppose that the danger is less when the virus has passed straight through to the liver tissue, than when there is in the portal vein a focus continually emitting fresh supplies of it, and able also to infect the peritoneum in its neighbourhood. In Mr. Morton's case again the abscess, though undoubtedly infective, was single, and was thus amenable to treatment.

Diagnosis.—This has rarely been made during life ; thus, at Guy's Hospital 2 cases only were diagnosed out of 20 (Bryant). The reason is that the symptoms are seldom complete. A physician would hardly venture to diagnose such a rare disease unless one of its known antecedents, of which appendicitis is the most common, was, or had recently been, present. When a patient has, or has lately had, appendicitis, or is suffering from some focus of suppuration within the abdomen, the appearance of symptoms of acute hepatic disease, together with those

of pyæmia, justify the diagnosis being made. The most important and constant hepatic symptoms are enlargement and tenderness. Pain is much less constant. Slight jaundice is present in rather less than half, about 40 per cent, of the cases. Signs of portal obstruction are seldom well marked ; the commonest is enlargement of the spleen, and this, as Dr. Langdon Brown says, is of considerable value if we can watch it develop. The general symptoms of pyæmia, including leucocytosis, are probably always present. But the cultivation of microbes from the blood is usually unsuccessful, for the infection is generally retained within the portal system. Peritonitis is a frequent complication, but its presence will probably rather mislead us than otherwise, as it will suggest that this is the substantive disease. When the symptoms are incomplete the diagnosis may be impossible.

Differential Diagnosis.—A subphrenic abscess above the liver produces much the same train of symptoms, but it is usually accompanied by much greater upward displacement of the diaphragm than is seen when there are multiple abscesses within the liver. Tropical abscess is a more chronic disease, and seldom produces true pyæmia ; there is usually a circumscribed local swelling below the ribs, or a more pronounced bulging of the ribs than in multiple abscess. Enteric fever sometimes produces a general condition not unlike the later stage of pylephlebitis, but it has points of distinction, the presence of the agglutination reaction, the absence of leucocytosis, and a much slower pulse. Simple cholangitis is not accompanied by such severe symptoms, but suppurative cholangitis may closely resemble pylephlebitis. In the former, however, the spleen does not enlarge and jaundice is more marked. Malaria and malignant disease must also be excluded.

Treatment.—Probably the most important treatment at present is preventive. Since portal pyæmia almost always depends upon a suppurative focus in the abdomen, and in nearly half the cases is due to appendicitis, a careful treatment of any such condition will greatly diminish the frequency, small even now, of portal pyæmia.

When the disease is established it is sometimes possible to discover and drain an abscess or abscesses in the liver as in the cases recorded by Dr. West and Mr. Morton. But nowadays such an operation would certainly be carried out by free incision of the abdominal wall or exposure of the surface of the liver, or else by a similar opening through the pleura and diaphragm, the details of which belong rather to Surgery than to Medicine. When this cannot be done, and especially when an abscess has formed in the vein itself, the treatment can hardly as yet be anything more than the relief of pain and the support of strength. The microbial nature of the infection gives us, indeed, ground for hope that we may sooner or later obtain fresh methods of treatment. But the difficulties are great ; on the one hand, the infection is usually confined to the portal area, the blood of which can only be examined by tapping the liver. Such a proceeding, unless the liver were actually exposed by an abdominal incision, would probably infect the peritoneum. On the

other hand, the disease is frequently due not to one, but to many forms of pathogenetic organisms. It seems within the bounds of possibility that we may in time overcome both these difficulties, and so may attack the infection by vaccines or antitoxic serums appropriate to the individual case. But haphazard injections of such remedies, without bacteriological evidence, have not been successful in the past, and are not likely to be more successful in the future.

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OCCULTION, BY STRICTURE, THROMBOSIS, OR PHLEBITIS, OF THE HEPATIC VEINS.—Occlusion of the hepatic veins is an uncommon condition which may arise from several causes. Its interest is almost entirely pathological, and according to Hess no case has been diagnosed during life. It will be best, therefore, to reverse the usual order, and to say what there is to say about the symptoms, for they are common to many different cases, and pass afterwards to the classification.

Symptoms.—These are only observed when the main trunks are affected. Nearly all the patients have complained of abdominal pain in the hepatic and epigastric regions. Sometimes it is very severe, and in one of Chiari's cases caused almost continuous vomiting for 14 hours. Ascites is nearly always present, but it was absent in Schüppel's, and not found during life in Chiari's second case. The fluid is usually opalescent, sometimes blood-stained, and occasionally purulent. In some cases the liver has been felt to be enlarged, but not in all, and occasionally the spleen has been felt below the ribs. Jaundice has been seen once or twice, but is exceptional. Anorexia, vomiting, and diarrhoea are common. The patients usually complain much of progressive weakness and feel very ill.

Duration.—These symptoms last usually but a few weeks. It is in most cases an acute condition, but Lichtenstern's patient, a man aged twenty, had from early youth been subject to attacks of abdominal pain, and Dr. Kelynack's, a woman of thirty-two, had had the same symptoms for two years. Yet in both of these the condition became much more severe a few weeks before death. In Chiari's first case the disease apparently existed less than a fortnight. So far as is known the condition is invariably fatal. Schüppel suspected it in a patient who recovered, but the diagnosis remained unproved.

Diagnosis.—If the first symptom is severe pain, the disease may for a time be thought to be strangulation of the intestine (Lichtenstern), or acute pancreatitis, or peritonitis due to perforation. But the onset is seldom so acute. The combination of pain and ascites, with vomiting but without jaundice, may be referred to tuberculous peritonitis, or to simple cirrhosis. Enlargement of the liver and spleen, when present, naturally makes the latter seem the more probable. But the affection which most closely resembles it in clinical features is thrombosis of the portal vein. The symptoms of the two are really identical.

Pathology.—The classification of these cases is difficult. Sometimes the occlusion is a mere accident in the course of another disease, the symptoms of which conceal any that the venous obstruction might have caused. Thus, branches of the hepatic veins may be rendered impervious by (i.) external pressure, by tumours such as hydatid cysts or new growths; (ii.) thrombosis, which may be due to (a) extension from the vena cava; (b) extension from local inflammation, such as hepatic abscess, suppurative pylephlebitis, and even occasionally simple cirrhosis; (c) an altered condition of blood favouring coagulation. In Dr. Newton Pitt's case many arteries and the right hepatic vein, in Schüppel's the superior longitudinal and both transverse sinuses of the dura mater, as well as hepatic veins, were blocked with thrombi; (d) the invasion of a vein by new growth; (e) the rupture into a vein of the so-called adenomas seen in some forms of cirrhosis.

But in other cases the obstruction of the hepatic veins forms the whole or the most important part of the patient's illness, and the symptoms above mentioned are well marked. These cases have been found to be due to various causes.

(1) A new growth, whether malignant or syphilitic, may compress or invade the main hepatic trunks, and even also the vena cava. In one case a large gumma had obliterated all these veins, so that their structure could not be traced through it, and projected into the right auricle (S. West). (2) More commonly the mouths of the veins are invaded and blocked by some form of inflammatory hyperplasia. It is impossible to separate these cases by any rigid distinction into external inflammation (periphlebitis) and internal (endophlebitis), since both forms are usually present together. Yet of the recorded cases which have been collected by Hess, some at any rate seem probably to have started within the vein, and others in the tissues outside it. (a) Some cases are due to extension of inflammation from tissues outside the liver. In a man aged fifty-two, who drank enormous quantities of gin, Budd found all the hepatic veins thick and opaque, and covered by a false membrane. There was what is now called polyserositis affecting the peritoneum, pericardium, and pleura, with thickening of the mediastinal tissues. There was some fibrosis of the liver. Frerichs saw a somewhat similar condition in a drunkard aged forty-five. In another case a scarred and contracted gastric ulcer was thought to have been the starting-point of the adhesions. (b) In other instances the inflammation seems to have

spread from the liver. A man of twenty-six, never strong, had noticed an enlargement in the epigastric region for two years. He was admitted with ascites, and died in six days. There was a diffuse monolobular and intercellular cirrhosis of the liver and adherent thrombi, with inflammation in and around the hepatic veins (Churton). A somewhat similar case in a boy aged thirteen is recorded by Dr. Lazarus-Barlow. Both of these were suspected to be due to congenital syphilis. A child, aged seventeen months, who up to that time had been well, had abdominal pain, then general swelling, and, lastly, ascites. She was twice tapped, and died. The liver was cirrhotic. The inferior vena cava was natural, except that slight dimples on its surface constituted the only indication of the spot where the hepatic veins should have opened. The orifices of the hepatic veins were quite closed by membrane and old adherent thrombi. Dr. Gee thought that had the condition been congenital the ductus venosus would not have closed. Rosenblatt (quoted by Chiari) thought that his case—the patient was a man of twenty-seven—had originated in a partial (left lobe) embryonic cirrhosis, either preventing the opening of the hepatic veins into the cava, or closing a communication already formed. (c) In other cases primary endophlebitis seems certainly to have existed. A man, aged twenty, seen by Lichtenstern, had been from boyhood subject to attacks of abdominal pain. He was suddenly seized with acute pain and diarrhoea and became very oedematous. There were great tympanites and some ascites. He died from oedema of the lungs. There were obliteration of the hepatic veins by endo- and peri-phlebitis, and some deposit in the vena cava also. He was not syphilitic or alcoholic. The liver was not cirrhotic and the capsule was natural. Chiari saw a similar case in a man twenty-nine years of age. In two women examined by Chiari the same conditions existed in the veins, but were ascribed to syphilis. In one of the patients, aged twenty-eight, there was a scar in the labium majus; the other, aged fifty-nine, had an aneurysm of the left ventricle. (d) Injury from repeated coughing is a cause suggested by Kretz. He thinks the liver hangs partly by its veins and that violent cough may produce slight tears in the coats of the vessels, leading to phlebitis. (e) Congenital malformation was thought by Penkert to be the cause of the appearances in his case, which much resembled Dr. Gee's. His patient was a boy, twenty-two months old, who had had ascites and enlargement of the liver for a few weeks before death. There was no primary cirrhosis. It is clear that much of this pathology is conjectural.

Morbid Anatomy.—The appearances are those of intense congestion. Parts of the liver are described as black and dripping with blood, the rest as like nutmeg. When not contracted by interstitial disease, the liver is enlarged. The portal branches sometimes contain thrombi. The stomach and intestines are sometimes deeply congested. The peritoneum sometimes shews a dense adhesive inflammation, but more often is affected secondarily, as in cirrhosis, with ascites. It is then slightly thickened and congested.

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ANEURYSM OF THE HEPATIC ARTERY is very rare. Mester in 1895 collected 20 cases, Grunert in 1903 increased the number to 35, and in 1908 Dr. Rolland collected and analysed 41 cases.

Etiology and Pathology.—Of 39 cases, 9 were in females, 30 in males. The proportion of women is here much greater than in aortic aneurysm. It is not easy to believe that great strain could be put upon the hepatic artery, and though in a few cases a blow or severe pressure seems to have been the cause, the greater number seem to own to no exciting cause from outside. They seem rather to resemble cerebral aneurysms than aortic. Grunert is of opinion that most of them are due to some infectious process, as out of 22 cases he finds 16 in which an infectious disease closely preceded the first symptoms of the aneurysm. Of these cases 4 were examples of osteomyelitis, and Bickhardt adds another, 4 were cases of pneumonia, and two of enteric. The other case recorded by Bickhardt was due to tuberculosis of the surrounding liver tissue which had spread to the wall of the artery. The age of incidence of these cases is rather in favour of Grunert's opinion; of 23 cases no less than 14 were under thirty, and six were under twenty years of age. In only 1 of his collected cases was the hepatic artery described as sclerotic.

Morbid Anatomy.—The hepatic artery runs forward for about an inch from the coeliac axis before it gives off its gastro-duodenal and pyloric branches, but there are no cases on record of an aneurysm on this part of the artery. The vessel then runs upwards and backwards in front of the foramen of Winslow until its division. In 13 cases the aneurysm occupied this part of the artery, in 8 cases it implicated the right branch alone, in 3 there was an aneurysm on each division, in 3 others there was one on the left branch alone. This is Grunert's statement from a total of 32 cases in which the necessary details were available. In three cases the aneurysm was intrahepatic. These aneurysms rarely become larger than a walnut. In 1 case there were no less than four small aneurysms.

Death is usually caused by rupture. Out of 25 such cases the rupture took place into the peritoneal cavity in 10 cases, into some part

of the bile passages in 10 cases, into the stomach twice, into the duodenum twice, and into the portal vein in 1 case. In 1 case, as above mentioned, the wall of the aneurysm was found to be infiltrated with tubercle, which had apparently spread from the liver tissue.

Symptoms, Course, and Progress.—The three chief symptoms are pain, haemorrhage, and jaundice, but none is constant. Pain is the most common, and usually the earliest; it generally occurs in severe attacks and is referred to the epigastrium. There is often tenderness. Haemorrhage is the second in importance. It is recurrent. Sometimes it takes place into the stomach, but more often into the duodenum; accordingly melaena is more common than haematemesis, and in one or two cases large clots marked with the impression of the valvulae conniventes have been passed from the bowel. Jaundice was stated to have been present in 16 out of 40 cases (Rolland). The tumour is hardly ever palpable, and pulsation has never once been felt through the abdominal wall, so that a pulsating tumour in that region is pretty certainly not a hepatic aneurysm; even at the four laparotomies, in which the tumour has been exposed, it has only once been seen or felt to pulsate (Kehr). Grunert thus describes an operation performed by Habs:—"In the attempt to pass a sound up the hepatic duct after the gall-bladder had been opened, a tight, elastic tumour as large as an apple was discovered; this tumour, which surrounded the hepatic duct on all sides and made the passage of the sound impossible, did not pulsate." The liver, however, is not infrequently enlarged, and may be pushed forward by the underlying aneurysm.

The condition has been known to exist for six years (5), but the average duration from the first appearance of symptoms is estimated by Grunert at three months and a half.

Diagnosis.—This has never yet been made during life, except after laparotomy. Even the presence of pain, haemorrhage, and jaundice is not sufficient ground for excluding duodenal or gastric ulcer, and in the absence of haemorrhage, the more probable cause of the pain and jaundice is biliary colic. In Grunert's case the diagnosis was actually rendered rather easier by the absence of characteristic symptoms. He writes:—"Compression of the hepatic duct, gall-stones, and duodenal ulcer were excluded by the absence of their characteristic symptoms; for there had never been severe colic or any haemorrhage. Pressure on the common bile-duct could be eliminated, because the gall-bladder had never been palpable. The only causes of obstruction considered were stenosis from the scar of an ulcer and tumour. Stenosis was contra-indicated by the varying character of the jaundice . . . and so the suggestion that there was a growth was left. This could not be malignant, or in the course of a year the general condition must have been more affected." In Kehr's case the man was cachectic, with a history of two years' illness, and of profuse haematemesis and jaundice in the past. The gall-bladder was enlarged, but not tender; the liver was not enlarged, and there was then no haematemesis or

jaundice. Kehr says that hepatic aneurysm was one of the possible diagnoses.

Treatment.—It is obvious that, as the condition has not been diagnosed before laparotomy, medical treatment has not been carried out. The hepatic artery has once been tied, by Kehr, for this condition, with success. An unexplained illness of this nature will probably suggest a laparotomy; if the possibility of hepatic aneurysm be kept in mind laparotomy perhaps may be undertaken with slightly greater readiness, and, if the tumour is diagnosed when seen, it does not appear to be very difficult to tie the artery in the lesser omentum.

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Rolland gives a complete bibliography, and an analysis of 40 cases besides his own.

W. P. H.

CONGESTION OF THE LIVER

By WILLIAM HUNTER, M.D., F.R.C.P.

SYNONYM.—*Hyperaemia of the Liver.*

Definition.—A pathological condition associated with a number of diseases, not itself constituting a disease, but conveniently considered separately on account of the size and importance of the organ; consisting in the presence of a large excess of blood within the blood-vessels of the liver; clinically characterised by a varying degree of enlargement of the organ beyond physiological limits and by disturbances of liver function; caused by two distinct sets of conditions, one of infective or toxic (gastro-intestinal) origin—"active" congestion, the other of mechanical (cardiac) origin—"passive" congestion, or chronic venous engorgement.

Varieties.—The condition known as "congestion of the liver" cannot be regarded as a distinct disease. In any circumstances the border-line between physiological and pathological hyperaemia of any organ is ill defined; and this must especially be the case in an organ subject, like the liver, to great physiological variations in the quantity of blood it contains. If therefore a pathological condition like congestion, common in varying degree to all organs alike, be dignified with the title of disease, it must be on some special ground, such as the size of the

organ or the importance of its functions, and the consequent gravity of the effects connected with disturbance of them. Examples of such organs we have in the case of the brain and spinal cord. It is only on this ground that congestion of the liver has any claim to be considered as a formal malady ; for it is always associated with and depends upon diseased conditions elsewhere—notably, for instance, upon congestion of the gastro-intestinal tract. In the case of the gastro-intestinal tract the effects of congestion are widespread and ill defined ; in the case of the liver they are concentrated, and thus arrest the attention alike of patient and medical observer. These effects in the liver occasion a distinct local distress, as well as more general symptoms referable to disturbances of its assimilative, antitoxic, and biliary functions.

Again, the liver is particularly subject to congestions, partly on account of the character and the richness of its double blood-supply ; partly on account of its situation at the outlet to the portal system on the one hand, and of its neighbourhood to the heart on the other. Thus it has to share in every congestive trouble arising throughout the extensive area from which the portal blood is drawn ; whilst its proximity to the heart renders it one of the first organs to be affected by any obstruction to the flow of blood through the right side of the heart.

According as the increase of blood is brought about by *increased inflow* through the portal vein, or *obstructed outflow* through the hepatic veins, it is possible to distinguish *two varieties of congestion of the liver*, different alike in their causes, their clinical features, and their pathology. Hence the distinction between them is of practical importance. The congestion due to obstructed outflow is rightly called *passive*, as it is brought about by mechanical causes, and is attended with corresponding lesions—such as dilatation of capillaries, fatty change, and atrophy of cells—the results of increased pressure. That connected with increased inflow, on the other hand, is in the first instance an exaggeration of the normal condition of the organ during the times of its activity ; it is the result of chemical and nervous influences, such as operate in health during digestion ; and the anatomical changes are also those of increased activity, and not of increased pressure. This form is therefore rightly called *active*. As an independent affection it is this latter form of congestion only that really needs consideration.

ACTIVE CONGESTION.—Etiology.—The two main groups of causes are—(i.) *non-infective*, connected with the character and quantity of the food taken and of the products formed in gastro-intestinal digestion ; (ii.) *infective*, the formation of toxic products by (a) organisms normally present in the alimentary tract, or (b) other superadded infections. The former group comprises the great majority of cases met with in this country, where the hepatic congestion is traceable to morbid congestions of the stomach and intestine arising from errors in food and drink, and the digestive and putrefactive disturbances connected therewith. The latter includes the cases, common rather in tropical climates, in which the congestion

seems to be due to some specific infective influence, as in malaria and dysentery (*vide* article "Tropical Liver," Vol. II. Part II. p. 571).

(i.) *Non-infective Influences.*—The most common causes of active congestion of the liver undoubtedly are gastric catarrh and associated intestinal congestions set up by undue indulgence in food and drink. It is most commonly found in persons who habitually eat and drink much and take little exercise. Rich and highly seasoned foods which tend to produce or aggravate the conditions of catarrh and congestion of the mucous membranes are potent for evil.

Excess in malt liquors, wines, or spirits is undoubtedly also a very potent cause of congestion, and more common perhaps than excess in eating alone. That these agents exert a directly injurious action on the liver itself is proved by the occurrence of cirrhosis of liver. It is in the habitual toper that the best-marked attacks of congestion of the liver are to be met with in this country.

Over-indulgence in liquids of any kind, especially if taken with food, also favours the occurrence of the condition in persons of plethoric habit of body.

Not only excess, however, but irregularities in the times of taking food, insufficient mastication, and other causes of gastric catarrh, will produce congestion of the liver in persons liable to it; for certain patients appear to have a proclivity to hepatic congestion. Such patients are usually of stoutish build of body, of phlegmatic habit, and of sallow, muddy, so-called "bilious" complexion. There is a want of tone about them generally, which seems especially to affect their portal vascular system. Causes which in ordinary persons would set up a temporary indigestion at worst, will in them produce well-marked congestion of the liver. Most of the above causes operate strongly at or near the middle age, when a sedentary life is more usual.

Congestion of the liver is frequently a premonitory sign of an attack of gout; and the connexion between these two conditions was insisted upon long ago, chiefly by English observers (Scudamore, Gairdner, Garrod).

The foregoing causes operate by producing and maintaining conditions of congestion and catarrh in the stomach and intestine. Among the rarer causes may be mentioned dilatation of the stomach, which, according to Bouchard, may set up active liver congestion. This association I have also had occasion to note.

(ii.) *Infective Conditions.*—In warm climates, malaria, dysentery, and intermittent fevers are active causes of congestion of the liver. To the same group also belong the various forms of febrile jaundice.

It is probable that in most if not in all these cases the influence on the liver is brought to bear through the intestines, as in dysentery; and that it differs from that operative in the foregoing group of cases in being of an infective nature.

The *influence of climate* in favouring congestion of the liver is fully considered in the article on "Tropical Liver" (Vol. II. Part II. p. 571), to which the reader should refer.

Lastly, there remain some other conditions which have been regarded as causes of congestion of the liver.

The first of these is *suppressed menstruation*, in connexion with which some degree of congestion is said not infrequently to occur; sometimes with jaundice. Four such cases of "menstrual jaundice" are described by Senator. This variety of congestion is usually met with either at the catamenial period or at the approach of the climacteric; and it has been supposed to arise directly from vasomotor disturbance. Perhaps these cases ought to be regarded as belonging to the large ill-defined group in which "congestion of the liver" is used as a convenient and popular name for ill-understood disorders.

In *diabetes mellitus*, also, some degree of congestion occurs. Since the time of Bernard it has often been assumed that in diabetes some disturbance of the central nervous system might be one of the factors operating through the liver to bring about this condition. A more probable explanation of the congestion of the liver in such cases appears to me to be the increased work thrown on the organ by the consumption of the large quantities of food and drink necessitated by the condition itself.

Exposure to cold or chills, especially in persons who have had malaria or dysentery, is undoubtedly a cause of acute congestion of the liver. This effect is, however, mainly seen in persons who have lived for a considerable time in the tropics.

Morbid Anatomy.—The anatomical changes found after death in cases of active congestion are ill marked. The liver is swollen, enlarged, dark in colour; and on section its vessels are found very full of blood. This overfilling is not limited to the central portion of the lobule, as in the "cardiac liver" (chronic congestion). The lobules may shew some appearances of fatty change; but the mottling (nutmeg appearance), so characteristic of the cardiac liver, is not seen. On microscopic examination the liver-cells are swollen and often fatty; or they shew some degrees of parenchymatous degeneration and cloudy swelling.

The changes as a whole are significant of over-activity, and differ from the atrophic and pressure changes presented by the "nutmeg" liver.

Symptoms.—The symptoms of active congestion group themselves into two classes: those connected with the congestion, gastro-intestinal or other, with which the congestion is associated; and those referable to the disturbances in the liver itself. The common symptoms are those of gastric or gastro-duodenal catarrh—headache, malaise, loss of appetite or sickness, bitter taste in mouth, coated tongue, constipation—to which are added a sense of discomfort, weight, or even actual pain and tenderness over the region of the liver itself; the patient at the same time usually presents the muddy complexion and the yellow eyes so characteristic of liver disorder. The pain and discomfort over the liver are aggravated by pressure or by movement; they may be affected even by pressure of the clothes. Not infrequently the pain is referred to the right shoulder.

The liver is found appreciably enlarged ; it projects below the costal margin and is tender to the touch.

There is usually a slight degree of jaundice ; in the group of cases depending on toxic influences it may be considerable, even intense.

The urine is high-coloured, concentrated, of higher specific gravity than normal, and usually loaded with urates ; not infrequently also it contains uric acid crystals. Bile pigment is usually absent, except in the presence of jaundice.

The nervous disturbances are not the least prominent and disagreeable, including as they do not only headache and feelings of giddiness and drowsiness, but also great irritability of temper and mental depression.

Clinical Varieties.—According to the severity and duration of the attack, two varieties are to be recognised—*acute*, met with in fevers, and marked by much constitutional disturbance ; *chronic*, in which the symptoms are more those of disorder of digestion, connected with long-standing habits as to food, drink, and exercise.

Diagnosis.—The diagnosis rests on a concurrence of symptoms of gastro-intestinal disturbance with enlargement of the liver, and pain and discomfort in the region of that organ. The distinction from acute hepatitis, such as occurs in hot climates, is mainly one of degree ; in acute hepatitis the symptoms are more severe, and it has been suggested that when the bodily temperature rises above 100° F. the condition should be regarded as inflammatory (Cantlie).

Prognosis.—The condition is not dangerous in itself. It derives its importance from its causes.

Treatment.—The indications in treatment are mainly two : (a) To correct the habits of life on which the condition mainly depends ; (b) To remove the gastro-intestinal conditions and the associated hyperaemia which prevails throughout the portal system.

(a) If the error be one of excess the food must be smaller in quantity, less bulky, and less stimulating in character, and the intervals between meals longer. In the choice of food regard must be had to the stomach, and only such food given as will be readily digested without giving rise to irritating products. Sauces and all dishes containing over-heated fats, such as entrées, pastries, and the like, should be avoided. Fat in any form should be taken sparingly. The safest meats are those roasted, or, in the case of fish, boiled or broiled.

If the immediate cause of the congestion be alcoholic excess, as it often is, alcohol in every form should be cut off for the time being. If alcohol be only one of the factors it should be taken in strict moderation, and only with meals. Indeed, the quantity of liquid of any kind taken with meals should be small ; liquids are better taken on an empty stomach between meals. Our object in these measures is to avoid undue dilution of the gastric juice during active digestion—to restrict the inflow of blood into the portal system and lessen the amount of digestive work to be done.

(b) In carrying out these measures we are doing much to carry out

the second indication of treatment; for by regulation of the diet we diminish and get rid of the gastric catarrh, with the associated hyperaëmia throughout the portal tract. Much can also be done in this direction by use of medicines, such as bismuth with alkalis and bitter tonics given before food; or dilute acids, especially nitro-hydrochloric acid with nux vomica, after food.

But our chief means of diminishing the hyperaëmia throughout the portal system is free depletion of this system by purgatives. At the same time the patient must be led to take more exercise. For the former purpose we prescribe the various saline purgative mineral waters—Carlsbad salts, preferably in effervescent form, Marienbad, Homburg, or Johannis—taken on an empty stomach in the morning, with an occasional pill at night time, containing one or more of such drugs as podophyllin, mercury in the form of blue pill, aloes or aloin, nux vomica, or rhubarb (compound pill). How much such measures are calculated to relieve the condition is shewn incidentally in cases in which a copious bleeding from piles is immediately followed by great relief to the more distressing liver symptoms, possibly even by appreciable diminution in size of the liver itself.

When, as often happens, the liability to such congestive attacks becomes a habit of life, the treatment becomes a much more difficult task. In addition to the foregoing measures, it is in such cases that great benefit is derived from periodic visits to such watering-places as Homburg, Carlsbad, Marienbad, or Vichy. The benefit thus obtained is partly due to the use of the various purgative waters, partly also to the more regular life and the more restricted diet to which patients, otherwise unamenable to advice, more readily conform.

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PASSIVE CONGESTION.—SYNONYMS: *Nutmeg Liver*; *Cyanotic Atrophy of Liver*; *Cardiac Liver*.—**Definition.**—A pathological condition consisting in an excess of blood within the liver, caused by obstruction to the outflow of blood from the organ, in the great majority of cases as the result of cardiac disease; characterised at first by enlargement of the liver, in the later stages by shrinking and atrophy, with symptoms of impeded portal circulation.

Etiology.—This form of congestion differs essentially from the one already considered in being of purely mechanical origin. It is the result of impeded outflow of blood from the hepatic veins, consequent on backward pressure of blood in the inferior vena cava. The conditions which lead to this are such as interfere with the free passage of blood through the heart, and include, therefore, all those lesions, whether of cardiac

or of pulmonary origin, which tend to functional incompetence of the right side of the heart. Of the cardiac conditions the most common is mitral disease, both dilatation and stenosis, especially the latter; but all other heart lesions, whether valvular or inflammatory, and degenerative alterations of the cardiac muscle, tend to produce this condition in proportion as they throw increase of work upon the right side of the heart, and ultimately weaken it.

Certain *pulmonary* conditions, in so far as they impede the circulation through the lungs and throw increased work upon the right side of the heart, also favour its production. The most common of these is general emphysema with chronic bronchitis. Other conditions are chronic interstitial pneumonia, congenital atelectasis, pneumonia, and compression of lungs, whether by pleuritic exudations (especially of the left side) or by intrathoracic tumours (aortic aneurysms, mediastinal tumours).

Lastly, in quite exceptional cases the obstruction to the outflow of blood from the liver may be produced by more local lesions—constriction or occlusion of the hepatic veins (*vide p. 150*), or narrowing of the vena cava above the junction of the hepatic veins by tumours in this region (aneurysms, enlargement of glands), or extensive effusions into the left pleura. The latter may push the mediastinum so much to the right as to bend the vena cava almost at a right angle.

Morbid Anatomy.—The liver is engorged with blood and greatly enlarged; and inasmuch as the cause of the hyperaemia is usually permanent (for example, valvular disease), the hyperaemia itself is permanent, and ultimately leads to permanent structural changes. The engorgement of the vessels especially affects the capillaries (sinusoids (Minot)) in the centre of the lobule in immediate relation with the hepatic veins. They become greatly dilated, the liver-cells around are shrunken and atrophied by pressure, and usually contain much haematoxin. The liver-cells disappear and their place is taken by haemorrhagic areas, and thrombosis may occur in the sinusoids near the central vein in advanced cases (Hart). From compression of the central zones the peripheral zones of the adjacent lobules may coalesce and produce a confused picture under the microscope (Géraudel). The centre of the lobule presents a deeply congested pigmented appearance; and, inasmuch as the cells in the outer zone of the lobule are usually fatty, there is a marked contrast between the congested and the fatty zones. On section the liver thus shews a mottled appearance, like that of a nutmeg on cross section—hence the title “nutmeg liver.”

In course of time other secondary changes ensue. The increased pressure leads to an increase of the connective tissue in the centre of the lobule, and eventually to a well-marked induration and shrinking of the liver substance. In the later stages of the condition, then, enlargement gives place to an atrophy and induration of the organ (cyanotic atrophy).

Symptoms.—The symptoms accompanying the above condition are mainly those of the cardiac or pulmonary condition giving rise to it; but there are in addition others more directly due to the liver itself. Chief

among these is the *enlargement of the liver*, sometimes recognisable only by percussion, at other times so great as easily to be made out by palpation. In severe cardiac cases it may be so great as to form a prominent swelling on the right side of the abdomen, extending a hand's-breadth or more below the costal margin ; it may pulsate synchronously with the heart's beat. In very rare instances the enlargement imitates malignant disease. The patient experiences a great *feeling of fulness or tension* in the right hypochondrium, aggravated by external pressure or forced respiratory movements, usually also much increased by lying upon the left side.

Gastro-intestinal symptoms are usually more or less marked. They are the result of the congestion produced throughout the whole portal tract by the obstruction to the outflow of blood from the liver. They take the form of disturbed digestion and impaired peristalsis, sometimes also of haemorrhoids.

Ascites is also common. In the early stages it is only a part of a general dropsy. In the later stages, when atrophy and induration of the liver occur, it may be the direct result of the state of the liver. A degree of ascites, then, out of proportion to the general dropsy may indicate cyanotic induration of the liver. When the brunt of the backward pressure falls on the liver the clinical aspect may closely resemble cirrhosis and has been spoken of as "hepatic asystole" (Hanot).

A more definite symptom of liver disorder is the occurrence of *jaundice*. A certain degree of jaundice is very common in severe cases, causing, with the cyanosis, the peculiar dusky green discolouration of face which such patients present. It is the result of obstruction, occasioned by congestion and tumefaction of the tissues and catarrhal swelling of the epithelium of the bile-ducts.

The urine has the characters of backward pressure in cardiac disease. In very rare instances leucine and tyrosine have been found in the urine (Dixon Mann), either from failure of the liver to deal with the amino acids absorbed from the alimentary canal or from autolysis of the liver.

The *course and duration* of these symptoms depend entirely on that of the conditions which give rise to the obstruction. In heart disease they are gradually established ; and they vary from time to time according to the capacity of the right ventricle. It is only when the condition has been so long established as to lead to induration and atrophy that it may be said to have an independent existence, causing, it may be, more or less permanent ascites. Short of this the condition cannot be said to be an independent one, or in itself dangerous to life.

Treatment.—The treatment is mainly, of course, that of the cardiac or pulmonary condition which gives rise to it. At the same time the local symptoms can be much relieved by diminishing the portal congestion, either indirectly by cathartics, or more directly by applying half a dozen leeches over the liver.

To fulfil the first indication, great benefit will be got by occasional doses of calonel, or of smaller and more regular doses of blue pill, often

in combination with digitalis. When given in repeated doses calomel acts in such cases not only as a cathartic, but as a powerful diuretic also. Vegetable aperients are also useful; podophyllin, rhubarb, aloes: also the various mineral salts, such as sulphate of sodium, sulphate of magnesium, or the mineral waters containing them—Carlsbad, Marienbad, Homburg, and others.

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PERIHEPATITIS

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BY this name we understand an inflammation of the peritoneal capsule of the liver. It may be acute or chronic.

ACUTE PERIHEPATITIS, unless traumatic, as, for example, after fracture of the ribs on the right side, is but an unimportant part of some other acute process, such as acute peritonitis, hepatic abscess, acute pleurisy, or acute pericarditis, and is therefore of little interest. The patient complains of pain in the region of the liver, especially when he breathes or coughs, and therefore the respiratory movements on the right side are limited. The muscles over the liver are rigid, the organ is very tender, and a peritoneal rub synchronous with respiration may be heard over it. Usually the symptoms are quite masked by the severity of those of the underlying cause, and a diagnosis is never complete unless this cause has been discovered.

CHRONIC PERIHEPATITIS is either universal—over the whole liver—or scattered in patches on its surface; in the latter case it is usually called local chronic perihepatitis. This variety has many causes which will readily suggest themselves to the reader; as instances, I may mention the local peritonitis over the liver which is merely part of a tuberculous or cancerous peritonitis; that which is seen around the gall-bladder in some cases of gall-stones; the thickening of the hepatic capsule seen in the neighbourhood of a gastric ulcer which has become adherent to the liver; the local peritonitis over a hepatic cancer, and the local peritonitis which radiates from a gumma or a depressed syphilitic scar on the surface of the liver. Local perihepatitis in patches is very common in marked backward pressure in pulmonary or cardiac disease; among eighteen examples of it, in ten there was either cardiac or pulmonary disease (12). Capsulitis of

the spleen is very commonly associated with local perihepatitis. Probably when so associated the splenic capsulitis hardly ever becomes universal. The thickened capsule cannot be readily peeled from the surface of the liver, save in quite exceptional cases ; and it commonly shews several little pits on its surface, which give it a meshed appearance. Usually no symptoms can be detected, but a rub can occasionally be felt or heard over the liver ; and perhaps local perihepatitis may sometimes explain the hepatic pain of which sufferers from diseases of the heart and lungs, or cirrhosis of the liver, often complain.

Universal chronic perihepatitis is a very different condition.

Morbid Anatomy.—The whole capsule becomes thick, opaque, and white, hence the name *Zuckergussleber*, applied to the liver by Curschmann, by which this lesion is known in Germany. This white jacket, which may be a quarter of an inch thick, easily peels off the subjacent liver, the surface of which is smooth ; and for some unexplained reason it is not uncommon to find the inferior edge of the liver folded up on to the anterior surface of the organ. In a case mentioned by Fagge the lower margin of the liver touched a point on the anterior surface that should have been $4\frac{1}{2}$ inches distant from it. As a result of the folding, the lower edge of the organ cannot be felt at all ; and, if the liver can be made out by tactile examination, the surface, at first taken for the lower edge, feels particularly thick and rounded. The upper and lower folds of peritoneum which form the posterior ligament of the liver become so thick that they are approximated, and the gall-bladder may be completely buried. Often little pits are to be seen on the surface of the thickened capsule. Occasionally the early stage of perihepatitis is met with in the post-mortem room, in patients who have died of some other affection ; then the liver is simply covered with a thin layer of white lymph which easily peels off. The thickened peritoneum consists of fibrous tissue undergoing hyaline degeneration in parts and arranged in horizontal laminae. There are often considerable adhesions between the liver and diaphragm, and this may explain why, when the perihepatitis, with the chronic peritonitis of which it is a part, is associated with similar chronic inflammation of the pleurae, it is the right pleura that is most often affected. In the same way some authors explain the frequency of chronic inflammation of the pericardium on the ground that the lymph-glands in the anterior mediastinum receive lymph from the peritoneal cavity. Doubtless a micro-organism is the cause of the trouble, but in most cases it is impossible to determine which micro-organism is the offender.

The liver with its thickened capsule generally weighs about the same as a healthy liver ; the organ is therefore a little atrophied. Opinions differ as to the condition of the liver in universal perihepatitis. Murchison states that perihepatitis leads to atrophy of it, and that "fibrous bands also pass from the thickened capsule into the interior of the liver, which on section presents a dense, smooth, uniform surface with the outline of the lobules more or less obliterated" ; but, as he goes on to say that this is especially seen in syphilis and long-standing

backward pressure from heart disease, there is little doubt that he is describing extreme cases of the patchy perihepatitis to which I have just alluded. Fagge, on the other hand, says the hepatic "tissue is commonly soft, and is very often loaded with fat. It is seldom cirrhotic, but there is sometimes an excess of white fibrous tissue in the course of the large portal vessels." This is what I have observed ; and among twenty-two consecutive cases of universal perihepatitis at Guy's Hospital I find the liver was never markedly cirrhotic ; its tissue was nearly always soft. All authors are agreed as to the rarity of genuine cirrhosis of the liver in association with universal perihepatitis. In two instances in which the patient had had syphilis it was lardaceous. Sometimes chronic pericardial adhesions and sometimes chronic renal disease with subsequent cardiac failure may be associated with chronic universal perihepatitis, and then the liver may be nutmeg.

The thickened capsule hardly ever exercises sufficient pressure in the transverse fissure to compress the bile-duct ; jaundice is extremely rare in perihepatitis, and I never heard of the gall-bladder being dilated. Many authors assume that, as ascites is very common in perihepatitis, the flow through the portal vein is impeded either by the pressure of the thickened capsule on the portal vein in the transverse fissure, or by its pressure on the liver as a whole ; but against this is the extreme rarity of jaundice, for it is difficult to believe that the increased pressure would always fall upon the portal system and never on the bile-ducts. Then, again, in a case of perihepatitis in which, at various times, nearly 800 pints of fluid had been withdrawn from the abdomen, I carefully dissected the portal vein, and could not find any evidence that it was dilated, or that it was constricted by the thickened capsule of the liver at the transverse fissure of the liver.

Polyorromenitis, polyserositis, multiple serositis, multiple progressive hyaloserositis, and Concato's disease are names (of which the first is to be preferred) used to describe cases in which not only is the peritoneal coat of the liver, together with the rest of the peritoneum, the seat of chronic inflammation, but so also are the pleurae and pericardium. In a severe case the pleural and pericardial inflammation implicates the mediastinal connective tissue, so that chronic mediastinitis is present as well. There are all degrees of this trouble ; the most common is for the pericardium, pleurae, and peritoneum (especially that over the liver) all to be affected. As pointed out by Dr. F. Taylor, in most of these cases the peritoneum is first attacked. Many are due to *Bacillus tuberculosis*, and others to pyogenetic micro-organisms, whilst others are associated with heart disease, but when all these have been considered there remains a group of which we do not know the cause. Kelly has drawn particular attention to the cases of polyorromenitis in which the pericardium is severely and earliest affected ; it is then firmly adherent, and the liver may be nutmeg. When the cardiac congestion of the liver has led to some increase of the fibrous tissue in the liver the unnecessary and cumbersome name pericarditic pseudo-cirrhosis has been given by Pick.

The consideration of pressure on the portal vein naturally leads us to that of the *conditions associated* with perihepatitis; for I shall shew that this universal chronic perihepatitis should, as it is almost always associated with a chronic general peritonitis, be regarded merely as a part of it; in this fact we have an explanation of the frequency of ascites and the rarity of jaundice. I took from the post-mortem records at Guy's Hospital forty consecutive cases of perihepatitis; eighteen were examples of partial and twenty-two of universal perihepatitis (12). Of the eighteen cases six were instances of peritonitis due either to tuberculosis or cancer, and the thickening of the capsule of the liver was merely part of the general peritonitis; of the remaining twelve one only had peritonitis, and, of the eleven left, eight are distinctly stated not to have had any peritonitis; in the remaining three the peritoneum is not mentioned. Turning now to the twenty-two cases of universal perihepatitis, in only two was there no peritonitis; in seventeen it is distinctly stated that there was peritonitis, and in the remaining three no mention is made of the peritoneum. The peritonitis was always chronic, and was never due to obvious tuberculosis or growth; it was always of that well-known variety in which the peritoneum becomes thickened and opaque (*vide* Vol. III. p. 949). Ascites is very frequent in simple chronic peritonitis, and I would argue that, constriction in the portal venous system being improbable, as we have just seen, the ascites which accompanies perihepatitis should be regarded as the result of the associated chronic peritonitis. This view is strongly supported by the fact that in the only two cases I have come across in which universal perihepatitis occurred without chronic peritonitis there was no ascites.

In the twenty-two cases of universal chronic perihepatitis, capsulitis of the spleen was found in fourteen, and in only two was it said to be absent. It was always universal, and should, like the perihepatitis, be looked upon merely as part of the general chronic peritonitis. In nineteen of the twenty-two cases the kidneys were granular, but other authors have not found the proportion so high. Nevertheless universal perihepatitis should probably be regarded as a sequel of interstitial nephritis, for the chronic peritonitis of which it is a part is a complication of this disease, and patients debilitated by renal disease are very liable to bacterial infection. As might be expected, considering the condition of the kidneys, in several of the nineteen there was some evidence of failure of the heart or lungs, and consequently sometimes the liver was nutmeg; in one case in which the cardiac failure was extreme there was jaundice, but this was the only instance of jaundice in perihepatitis. In four cases there was gout; in one more its presence was doubtful; in two others there was a strong family history of it; and in six cases there was a history of alcoholic excess: but it is particularly noteworthy that in none of these cases was there any marked cirrhosis,—in fact, in many of them it is distinctly stated that the liver was soft. In three instances syphilis was a very prominent feature, and this disease was probably the cause of the perihepatitis in those two patients in whom

no chronic peritonitis was present. So many cases of chronic peritonitis are tuberculous that the suggestion has been made that the tubercle bacillus is the cause of universal perihepatitis here described, but all the evidence is against this view, for generally the most careful post-mortem examination fails to reveal tuberculous lesions elsewhere or bacilli in the peritoneum. Many instances of universal perihepatitis are only part of a polyorromenitis, but in others the chronic inflammation is confined to the peritoneum.

The average age at death in twenty-two cases of universal chronic perihepatitis was $47\frac{1}{2}$ years; the youngest was 29, the eldest 68. The proportion of males to females was as 13 to 8, but others have found the numbers in the two sexes more nearly equal.

The symptoms need not detain us long. We often find albuminuria and other evidence of chronic interstitial nephritis; secondly, the liver is rarely enlarged, and the edge, if it can be detected at all, is thick, uniform, and felt just under the ribs; thirdly, there are the signs of chronic peritonitis (*vide Vol. III. p. 952*). The ascitic fluid, which usually collects gradually, soon makes the abdomen dull to percussion, even at the umbilicus, if the shortening of the mesentery draws the intestines back to the spine. The ascitic fluid is sometimes loculated between the matted intestines, and then the diagnosis may be very difficult; but commonly it presents the ordinary signs of ascites, and it is particularly characteristic of it that it re-accumulates quickly, often at the rate of a pint a day, after paracentesis: thus, the abdomen may be tapped several times, about once every fortnight or three weeks towards the end, before the patient dies from exhaustion. A sailor was under my care in Guy's Hospital; from December 25, 1885, to August 4, 1887, he was tapped thirty-five times, and the total amount of fluid withdrawn was 790 pints; the largest quantity taken out at any time was $31\frac{1}{2}$ pints, and the average was about 23 pints. After death he was found to have perihepatitis, chronic peritonitis, interstitial nephritis, and general lardaceous disease. As is usually the case, the fluid was clear and straw-coloured, and contained albumin. A woman under my care was tapped seventy times, and nearly 2000 pints were withdrawn, but so many tappings as thirty or seventy are quite exceptional. Oedema of the feet may be present, due sometimes to renal, pleuritic, or cardiac disease, and sometimes, perhaps, to pressure of the thickened peritoneum on the vena cava.

Diagnosis.—The common difficulty is to distinguish between perihepatitis and cirrhosis with ascites. If jaundice be present the patient almost certainly has cirrhosis; if the signs of chronic peritonitis are well marked, the presumption is much in favour of perihepatitis; but chronic peritonitis may be associated with cirrhosis. The main distinction is, that in cirrhosis the ascitic fluid, from the first, collects quickly, and the supervention of ascites—at any rate in sufficient quantity to require tapping—almost always means that the end is not far off; in cirrhosis the patient rarely lives long enough after the first tapping for a second to be necessary, but in chronic peritonitis with perihepatitis he does not

usually sink till after the abdomen has been tapped several times. I have published a series of thirty-four cases illustrating these points (11). Ten suffered from cirrhosis with ascites and died before tapping was necessary ; the average duration of life after enlargement of the abdomen was first noticed was only eight weeks. There were fourteen cases of cirrhosis in which paracentesis was performed. Here also the average duration of life after enlargement of the abdomen was first noticed was eight weeks ; no patient survived the first tapping long enough for a second tapping to be necessary. The remaining ten of my cases were those which were regarded during life as having cirrhosis, but were tapped oftener than once ; of these, in four the post-mortem examination proved the diagnosis to be wrong, one turning out to be a case of colloid disease of the peritoneum, and each of the other three had chronic peritonitis and perihepatitis : the remaining six had peritonitis, more or less chronic, associated with the cirrhosis.

Since I collected these cases I have seen two undoubted cases of uncomplicated cirrhosis in which life continued long enough to render a second paracentesis necessary ; but I have also seen several cases, diagnosed as cirrhosis, which had been tapped several times, but in which it was found that the diagnosis was incorrect, for they had no cirrhosis, but chronic peritonitis with perihepatitis. This opinion as to the extreme gravity of ascites in cirrhosis has been confirmed by Drs. Campbell Thomson and Ramsbottom. Fagge states there is one fatal case of ascites from perihepatitis to every five fatal cases of ascites from cirrhosis.

Treatment is of little avail. Paracentesis must be performed when necessary ; perhaps iodide of potassium is of use. To some extent the collection of fluid can be restrained by the use of diuretics, and of these the best is copaiba resin ; fifteen grains three times a day may be given in a cachet or suspended. Unfortunately it often causes nausea, and if so the diuretic pill containing a grain of each of powdered squill, powdered digitalis, and blue pill may be tried. In one case I tried leaving a tube for some time in the abdominal cavity to let the fluid run out as it formed, but this method did not prove of any benefit.

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CIRRHOSIS OF THE LIVER

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General Considerations.—The name cirrhosis comprises a group of diseases of the liver. Though they differ widely in their causation and clinical importance, they have this feature in common, that the organ becomes permeated in some degree by a newly developed fibrous tissue. The word cirrhosis, which, from the tawny yellow colour assumed by the hepatic tissue, was originally given to a common form of the disease (Laennec), is now in general use to denote any fibroid change in the liver. With this fibrosis there is associated a varying degree of cell-degeneration, to which the symptoms of the disease are partly attributable.

The disease is of common occurrence. The annual death-rate from this cause per million living in England and Wales rose considerably from 1871 to 1900, reaching 134·6 in the last year, but in the quinquennium 1901-5 a fall to 121·2 occurred. In 1905 there were 4008 deaths registered in England and Wales as due to this disease.

Classification.—(a) *Anatomical.*—The new fibrous tissue is distributed in various ways. (1) In the most common variety of the disease it forms a coarse network which permeates the whole liver and encloses in each mesh a varying number of lobules (multilobular). (2) In a less common variety a finer network tends to surround individual lobules (unilobular), and in this form especially a plexus of bile-ducts, apparently newly formed, is often present around the lobules. (3) In another form the new tissue penetrates the lobules themselves, surrounding and isolating individual cells or groups of cells (pericellular or intralobular). (4) Sometimes, though the predominant pattern is multilobular, the types are mixed, the unilobular and to a less extent the pericellular distribution being associated with it. Such an anatomical classification, however, is not applicable at the bedside.

(b) *Clinical.*—The ideal classification based on the causation of the various forms cannot be carried out owing to the gaps in our knowledge. For clinical use it is impossible to go farther than to differentiate the two principal types of the disease:—(1) Portal cirrhosis, to which in nearly all cases the terms "alcoholic" and "multilobular" may be applied, the chief features being the decreased size or moderate enlargement of the liver, the tendency to haematemesis and ascites, and the rarity and unimportance of jaundice; (2) Hypertrophic biliary cirrhosis, a disease characterised by its long duration, the presence of chronic jaundice, enlargement of the liver and of the spleen, and attacks of abdominal pain with pyrexia (crises), and by the absence of persistent ascites or signs of portal venous obstruction (*vide p. 185*).

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PORTAL CIRRHOSIS.—SYNONYMS : *Laennec's Cirrhosis; Alcoholic, Multi-lobular Cirrhosis; Hobnailed Liver.*

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Etiology.—In adults the disease is about three times as common in males as in females, but in the rarer form occurring in children the sex-incidence is uncertain. As regards the common form which is due to alcoholic excess, the chief incidence is in late middle life, and the average age at death is about 50. Publicans and commercial travellers are especially liable to the disease, and this extra risk is taken into consideration in insurance work. Heredity plays a part only in so far as an alcoholic tendency may shew itself in a family-stock, but it is curious that, as regards children, more than one member of a family may be affected even when there is no suspicion of an alcoholic origin. Though alcohol must be regarded as the main cause of cirrhosis, the distribution of cirrhosis does not by any means correspond with that of alcoholism. The annual death-rate per million living from cirrhosis (of all kinds) in Scotland is at the present time less than half that in England and Wales.

It can hardly be doubted that portal cirrhosis is the result of some poison conveyed to the liver by the blood. Theoretically such poison may be conveyed by the portal vein or by the hepatic artery. The anatomical appearance and the clinical evidence indicate the portal vein as the main channel of entrance, but it is possible, as will be shewn later, that in some few cases damage is done from the arterial side. As regards the nature of the poison, it is beyond question that the excessive use of alcohol is by far the most common cause of cirrhosis, and that if alcohol did not exist portal cirrhosis would be a rare disease.

(a) *Alcoholic Cirrhosis.*—All forms of alcohol can produce cirrhosis, but spirits are more potent than wine or beer. But though alcohol may be truly described as the predominant cause of the disease, it is open to question whether its action on the liver is direct and immediate, or whether some other factor is intermediate or conjoined. And the view is widely held that alcohol should be regarded not as the immediate cause, but rather as predisposing to, or assisting the action of some other poisonous agent which is not yet actually determined. This doubt as to the real connexion between alcoholism and cirrhosis arises from three sets of facts. In the first place, the amount of alcohol necessary to produce the disease varies greatly in different individuals, even when allowance is made for the different interpretations which may be placed on such indefinite terms as "hard," "free," and "moderate" drinking. Moreover, it is clear that cirrhosis is by no means a common result of habitual drunkenness. In fact, the common statement of the alcoholic cirrhotic patient that he has never been drunk is usually true. In the second place, some importance must be attached to the almost uniform failure to produce cirrhosis in the lower animals by administration of alcohol, the resulting change being cell-degeneration rather than fibrosis. And, thirdly, it is certain that a portal

cirrhosis differing in no particular, anatomical or clinical, from the alcoholic form may arise when an antecedent history of alcohol is certainly absent. As regards the apparent discrepancy between the dosage and the morbid result, it may reasonably be attributed to the different susceptibility of individuals, such as is observed in the therapeutic use of many poisons. It is possible also that the degree of dilution of the alcohol and the relation of its ingestion to the taking of food may have some influence in varying the result. As regards the comparative failure to produce cirrhosis experimentally in the lower animals, it may be doubted whether the concomitant conditions in the cases of the drinking man and the alcohol-poisoned animal are sufficiently similar to justify a conclusion. But the third point, the occurrence of a non-alcoholic portal cirrhosis, has much greater strength as suggesting that the relation between alcohol and cirrhosis is not simple and direct. These points of doubt have led to various hypotheses : (1) that the disease is not due to the ethylic alcohol, but to other constituents or adulterants of the drink, such as sulphate of potassium or the higher alcohols. It is not unlikely that alcohols other than ethylic may at any rate aggravate the result. (2) That there is an intermediate factor in the organic acids set free by fermentation in the alimentary tract of the alcoholic patient. (3) That alcohol produces its effect by inhibiting that function of the liver by which it deals with the bacterial products, normal or abnormal, conveyed to it from the gastro-intestinal canal. On this hypothesis there is then a twofold causation, alcoholic and bacterial. This hypothesis has the advantage of being applicable also to the non-alcoholic disease, for it is not improbable that in the non-alcoholic as in the alcoholic cirrhosis the exciting cause is of bacterial origin. And it is conceivable that congenital susceptibility or want of resistance in the liver (possibly parasyphilitic, *vide p. 202*) may in children play the disposing part which is taken by alcohol in adults.

(b) *Non-alcoholic Cirrhosis*.—It is not always easy to elicit a correct history of habits as regards the taking of alcohol, and even in young children it is sometimes found that spirits or beer have been administered to them by their parents. But it is beyond question that a non-alcoholic portal cirrhosis is occasionally met with in adults, more commonly in children ; and, further, the disease occurs among temperate or abstaining people, such as Brahmins and Mohammedans. It has been suggested that in these Eastern races curry, ginger, pepper, and the like may play the part of alcohol in Western countries. But in children of this country no article of diet save vinegar can be indicated as a possible cause. The evidence, indeed, supports a bacterial rather than a dietetic origin. On the experimental side the injection of sterilised cultures of *Bacillus pyocyanus* into the portal vein has been found to produce small-celled infiltration in the portal canals. The introduction of cultures of *Staphylococcus pyogenes aureus* into the alimentary canal has set up cirrhosis. There is evidence also from the pathological side that the liver may suffer from contact with bacterial toxins. The focal necroses which are found occasionally in the liver in enteric fever may be

attributed to the action of conveyed bacterial products. A similar change has also been found in some general infections, such as scarlet fever, measles, small-pox, diphtheria, and pneumonia. There is thus some evidence to support the hypothesis of a bacterial toxic origin. There is little or no evidence to warrant a belief in origination by infection of the liver with living bacteria, and all observations on this point are vitiated by the knowledge that after death from any cause living colon bacilli may be found in the hepatic capillaries.

The difficulty in tracing the origin of cirrhosis in children is increased because when the child comes under observation the disease is usually far advanced and the past history has become obscure. It is possible that a progressive cirrhotic process may be initiated by comparatively slight damage at some earlier date, just as a case of chronic nephritis may come before us in which no evidence of an acute onset can be obtained. In some cases there has been a definite history of preceding illness suggesting a bacterial origin, e.g. a child aged three years was admitted into St. Thomas's Hospital in 1889 with a history of measles and whooping-cough in the previous year, but of no other illness. For three days before admission she had been feverish, sick, and constipated. Then she became jaundiced. For the next two months she had a severe febrile illness with jaundice and progressive enlargement of the liver, of which the edge reached the umbilicus, the spleen not being palpable. She slowly recovered and left the hospital a month later with the liver still enlarged, but below its maximum size, the jaundice having disappeared. Neither before nor after this illness had the child had any alcohol. After some years of good health she was again admitted in 1897 with slight jaundice, the liver indurated, with its edge 2 inches below the costal margin, spleen palpable, slight ascites, and a large network of abdominal veins. In 1898 she was again admitted and died from haematemesis. Post-mortem, the naked-eye, and microscopical examination shewed a typical hobnailed liver, with advanced cirrhosis of the common multilobular type.

As a result of repeated attacks of malaria, degenerative changes in the cells and some fibrous hyperplasia in the portal canals may occur, but it is doubtful whether cirrhosis in the clinical sense ever arises from this cause. It is described, however, by French writers (Kelsch and Kiener). Certain minor forms of fibrosis occur under other conditions, but the change does not reach such a degree as to produce recognisable symptoms. Thus, a deposit of tubercles in the liver may be accompanied by a definite though slight degree of hyperplasia of the interstitial tissue in the portal canals; and this event is most common in association with a chronic tuberculous peritonitis (Hanot and Gilbert). The common enlargement of the liver in rickets has been occasionally found associated with a similar slight increase in the portal connective tissue. Finally, a cirrhosis, sometimes of a high degree, may result from the absence or atresia of the common bile-duct, which is occasionally met with in new-born infants (see p. 105). Life, in such cases, is seldom prolonged beyond a few months,

and death occurs from the jaundice rather than from the cirrhosis ; yet the latter may be sufficient to give rise to ascites. Apart from this it does not appear that a true portal cirrhosis arises as a result of biliary obstruction (*vide* p. 194). Syphilis plays no direct part in the production of cirrhosis, though it is possible that it may have a remote influence (parasymphilitic), especially in children. It is generally agreed that cirrhosis does not result from the venous engorgement of the liver which accompanies chronic cardiac and pulmonary disease.

Morbid Anatomy.—The liver is often reduced in size, but in many cases it retains its normal dimensions, and sometimes it is slightly enlarged, so that it may be easily felt during life. If a patient is seen with the signs and symptoms of advanced cirrhosis, and the liver is large enough to be felt in the abdomen, it is exceptional for any diminution in its size to be observed at a subsequent period. Some variation in size, however, is occasionally noted, and in a few instances, mostly in children, a progressive reduction in size takes place in the course of the illness. The weight of the hepatic tissue is increased by the cirrhotic process ; thus, though the liver is often diminished in bulk, its weight is seldom below that of the healthy organ. Its weight may, however, fall to 30 oz. or even less ; on the other hand, it may rise to 80, especially if its tissue be fatty. A series of 100 consecutive cases in adults taken from the records of St. Thomas's Hospital shews a minimum of 32 oz., a maximum of 74 oz., and an average of 52 oz. The average weight appears to be rather less in those dying directly from cirrhosis than in patients with latent cirrhosis who die from intercurrent disease.

From contraction of the new fibrous tissue there is commonly some alteration in the shape of the liver, especially when there is much diminution in size. Its sharp edge becomes blunter, or the whole organ may tend to become globular ; the left lobe is often more affected than the right, and may be reduced to a small triangular appendage. The peritoneal covering is usually much thickened, and is often fixed to the diaphragm, and perhaps to adjacent organs, by close adhesions or tough fibrous bands. There may be evidence also of the extension of this chronic inflammatory process over the whole or a large part of the peritoneum, which may be found whitened, thickened, and opaque. Whether the liver be of normal size, or small, or enlarged, both the natural and the cut surfaces of the organ in this form of cirrhosis are either covered with minute granulations, or studded with nodules varying in size from a pin's head to a pea. The cut surface especially presents the appearance of rounded islets of yellow or yellowish-brown hepatic substance surrounded by grey or greyish-red bands of fibrous tissue, both of which elements can be easily recognised with the naked eye. The substance of the organ is always exceedingly tough and hard, and the induration is greater than in any other form of cirrhosis.

There is considerable obstruction to the flow of blood in the portal vein, which may be dilated. In rare cases the stagnation is such that thrombosis has occurred in its main trunk and branches. A

common manifestation of this portal obstruction is the dilatation of some or all of the vessels which form the points of communication between the portal and the general venous systems. The vessels by which anastomosis is effected become dilated and even varicose, and the results are of considerable importance. There are three important points where this effect is produced :—(1) The plexus of veins at the cardiac end of the stomach communicates with a similar plexus in the lower end of the oesophagus, the vessels of which open into the azygos veins. Consequently in many cases of cirrhosis there is extreme dilatation of the veins in the lower three or four inches of the oesophagus, and longitudinal submucous vessels, up to a quarter of an inch in diameter, may be readily demonstrated there by means of injection or inflation with air. (2) One or more small veins (parumbilical) constantly run from the left division of the portal vein in the round ligament alongside of the obliterated umbilical vein to the umbilicus, where they communicate with the epigastric system. It is common, as a result of the portal obstruction, to find a large vein developed here, which often reaches the size of a crow-quill. A much larger size has indeed been recorded. (3) Finally, there is a variable degree of communication between the inferior mesenteric and haemorrhoidal veins. Other less important communications exist by which some of the blood may be diverted. There are the minor accessory portal veins of Sappey, which lie in the areolar tissue and peritoneal folds around the liver, and communicate on the one hand with the portal system, and on the other with the phrenic veins. In some cases enlarged vessels are visible after death on the under surface of the diaphragm, and this means of relief to the portal system may be aided when the liver is firmly adherent to the diaphragm. There is, moreover, some slight communication between the veins of the pancreas, duodenum, colon and rectum, and the retroperitoneal veins. A direct consequence of the passage of blood from the portal vein, by the parumbilical vein, to the epigastric system is the occasional appearance of a network of dilated superficial veins around the umbilicus. More commonly a few large vessels are seen running from the neighbourhood of the umbilicus downwards to the inguinal regions, upwards to the costal margin, and perhaps extending to the lower part of the thorax. In connexion with the dilatation of this parumbilical vein, it may be mentioned that a continuous venous murmur may occasionally be heard with the stethoscope immediately below the ensiform cartilage. The sinuous line of distended venules, which is often seen round the lower ribs along the line of attachment of the diaphragm, may be equally present in health ; it has no special significance in this connexion. The formation of haemorrhoids is too common a malady to be of great diagnostic importance, and it is not especially frequent in cirrhosis.

Microscopical examination of a liver in an early stage of cirrhosis shews clear evidence of inflammatory change in the tracts of connective tissue which support the ramification of the portal vein throughout the whole organ. These so-called portal canals are seen to be packed with con-

nective-tissue cells in a state of active proliferation. Here and there columns of such fibrifying tissue may be seen advancing between the hepatic lobules; and by the junction of such columns a wide-meshed network of developing fibrous tissue comes into being throughout the whole organ. In the late stage in which the examination is commonly made, this network is seen to consist of dense fibrous tissue which may be still richly nucleated in parts, but has generally lost the highly cellular character seen at an earlier period. It has been shewn that there is an increase also in the amount of elastic tissue. The main portal branches, which at an early stage are often widely dilated, become narrowed and compressed by the contraction of the new tissue in which they run. This new tissue, however, is by no means anaemic; for it can be shewn by injection from the hepatic artery that it is richly supplied with capillaries in connexion with that vessel; and it is probably due to this accessory blood-supply that the functions of the liver are so little interfered with. In some cases there is an apparent development of a few new bile-ducts in the strands of the fibrous tissue.

The nodules of hepatic tissue, which are contained in the meshes of this fibrous tissue, consist of six to ten lobules compressed together. Here and there also a single lobule or a single group of pigmented hepatic cells may often be seen as an islet in a broad fibrous strand, and in some cases areas of unilobular and pericellular cirrhosis are added to the prevailing multilobular pattern. Occasionally numerous so-called adenomas are seen, spherical masses surrounded by fibrous tissue, in which the hepatic cells have lost their normal arrangement, being disposed in a circular manner around a common centre or sometimes tending to form tubules. These are commonly regarded as evidence of a compensatory hyperplasia. In advanced cirrhosis the liver-cells are invariably degenerate, finely granular, or may shew coarse pigment granules. Often large fat-globules are a prominent feature. In the condition known as bronzed diabetes (see Vol. III. p. 183) the cells contain a brownish-yellow, iron-holding pigment, which is also seen in the endothelial cells lining the vessels, the connective-tissue cells, and the fibrous tissue. In rare cases, analogous to anthracosis of the lungs, the cells contain carbonaceous granules.

There is thus in cirrhosis both a degeneration of the hepatic cells and a development of new fibrous tissue; and it is by no means certain whether either of these changes is dependent on the other, or whether both changes are concomitant effects of one cause. It has been argued that the hyperplasia of the connective tissue is consecutive to a primary degeneration of the hepatic cells and dependent upon it; that it is such a hyperplasia, in fact, as is known to occur around degenerate and disused structures in all parts of the body. And in favour of this view, that the cell-degeneration is the exciting cause and not the effect of the fibrous overgrowth, it is pointed out that, although there is undoubtedly a high degree of pressure exerted upon the liver-cells, yet, inasmuch as the development of new vessels from the hepatic artery takes place step by

step with the growth of the new fibrous tissue, the blood-supply is still ample, and there is not that mechanical anaemia present which would be likely to cause such an extreme cellular degeneration. On the other hand, if specimens of early cirrhosis are examined from cases in which death has occurred from some other cause, no doubt can be entertained that the interstitial change is essentially an inflammatory one, and that it has its starting-point around the main branches of the portal vein at a time when the appearance of degeneration of the hepatic tissue proper is either scanty or absent. It is probable, indeed, that the cell-degeneration and the fibrous hyperplasia are both the result of the causative poison, and it is possible that in some cases in an early stage either result may overshadow the other.

There is usually evidence of venous engorgement in the whole area drained by the portal vein. The *spleen* is moderately enlarged, the average weight being about 10 oz. Its capsule is often thick and white, and it may be firmly adherent. Its substance is generally somewhat indurated. No doubt the increased venous pressure may partly account for its enlargement, but it is probable that the toxæmia contributes to the swelling. It is noteworthy in this relation that the spleen may shew progressive enlargement after the successful performance of the Talmamorison operation. The pancreas is commonly enlarged and indurated. The heart is frequently dilated and its muscle is soft and degenerate. The kidneys often shew fibrosis and a granular surface, perhaps in 20 per cent of cases, but epithelial change in them is comparatively rare. Arteriosclerosis is commonly present, but it has no special significance. Finally, in a few cases in which the clinical history and signs have not differed from those of common portal cirrhosis, carcinoma is found after death to be present in the cirrhotic liver. It is probable that the cirrhosis is here the primary change (*vide p. 216*).

Symptoms and Signs.—From what has been said as to the morbid process in the liver, it can be readily understood that the symptoms attending the early stage of cirrhosis are usually slight and equivocal. The more severe and distinctive symptoms do not appear until the new fibrous tissue has begun to compress the branches of the portal vein. In this early stage the patient is liable to dyspepsia with nausea or vomiting, especially in the morning. The appetite fails, being often better in the later than in the earlier half of the day; the tongue becomes furred; there is a sensation of heaviness or distension after meals, and gaseous eructations are of frequent occurrence. The bowels become irregular, at one time costive, at another time loose, and perhaps slight yellowness of the conjunctivæ may be noticed from time to time. Such symptoms may, of course, be merely the direct effect of alcoholic excess upon the stomach and intestinal canal; but their occurrence and persistence in a person who has been addicted to alcohol for some considerable time are sufficient to suggest the presence of cirrhosis in an early stage. Oedema of the shins is common enough in the late stages of the disease, but it occurs also in this early pre-ascitic stage with sufficient frequency to make it of

use in diagnosis. It is at this stage at any rate a toxic phenomenon and not the result of pressure on the inferior vena cava. The suspicion of cirrhosis would be strongly confirmed if at the same time some palpable enlargement of the liver should be detected. Cirrhosis in an early stage is often found unexpectedly in the bodies of those who have died from accident or other disease. From post-mortem work, Dr. Rolleston puts the number of those so dying with latent cirrhosis as 50 per cent of all cases of cirrhosis.

As the morbid process in the liver continues, the obstruction to the portal circulation increases in degree. A definite train of signs and symptoms ensues, some of which are the direct result of the portal obstruction, whilst others are the consequence of the impairment of the hepatic function. It is in this stage that the disease is commonly recognised for the first time. One result of the portal obstruction is the state of passive hyperaemia in which the stomach and intestines are maintained. Upon this there follows a very constant and persistent catarrhal condition of the mucous membrane. Digestion is imperfect, gastric fermentation and flatulence are common, and there is often nausea or vomiting in the morning, which is probably attributable to the mucus accumulated in the stomach during the night. The action of the bowels is also irregular; the motions are often pale and unformed, and diarrhoea is at times profuse and uncontrollable. Indirectly related to the portal obstruction is the common occurrence of haematemesis, or melaena, or both. It is possible that a general oozing from the congested capillaries of the stomach may be the source of the smaller quantities of altered blood which are sometimes vomited. Minute erosions of the gastric mucosa are sometimes the source. But it is probable that the larger haemorrhages are due to ulceration or rupture of one of the varicose veins already described as lying in the walls of the cardiac end of the stomach, and more especially in the lower end of the oesophagus. In the former situation punched-out ulcers have been found communicating with a vein, but the latter is probably by far the most frequent site of profuse haemorrhage. The haemorrhage may be very profuse and may be quickly fatal, as may be understood from the size of these oesophageal varices. More than four pints of venous blood may be lost in this way, and the bleeding may recur at intervals of a day or two until death results. In most cases, however, the haematemesis, though fairly profuse, is not so alarming; and many months or even years may elapse before death occurs. The patient may even experience relief from the haemorrhage. Haematemesis may occur at a very early stage, at a time when there has been no failure of health. If there have been previously only some ill-defined gastric symptoms, it may be difficult to distinguish between cirrhosis and a duodenal or gastric ulcer. Haematemesis occurs in less than one-fourth of patients dying from cirrhosis. Melaena is not uncommon. The blood may be shed from an ulcer or from distended capillaries in the bowel, but in most cases it is a relic of oesophageal or gastric haemorrhage.

Ascites occurs in at least 50 per cent of the cases. It is a late event, and consequently on its appearance the prognosis at once becomes grave. It may appear with great suddenness, as if some trifling event such as chill had precipitated it, but its onset is usually gradual. The ascitic fluid is clear, straw-coloured, and alkaline, with a specific gravity varying between 1010 and 1015 ; it contains from 0·4 to 3·0 per cent of protein, and it either has no power of coagulation or it slowly deposits a very light clot. If there be any coexistent peritonitis, the percentage of protein and the power of spontaneous coagulation are thereby proportionately increased. A trace of sugar is occasionally found in it. As regards the cytology of the fluid, endothelial cells are usually in the majority, amounting to 60-90 per cent, the remainder being chiefly polymorphonuclear cells, but in a few cases lymphocytes outnumber the latter, and in these a tuberculous infection has possibly been present. Very rarely the fluid is chyliform, the lactescence being due not to chyle, but to products of cell-degeneration. Haemorrhagic ascites is another rare occurrence. The amount of fluid varies greatly, but if it be not removed by paracentesis it may reach the enormous quantity of four or five gallons. It may accumulate so slowly that many months may elapse, after its first recognition, before paracentesis becomes necessary ; or it may accumulate so rapidly that as much as thirty-four pints of fluid may be removed within five weeks of a previous tapping by which the abdomen had been emptied as far as possible. Ascites is doubtless mainly dependent on the increased pressure in the portal vein, but the suddenness with which it may supervene at a late stage of a long illness signifies that it is not entirely of mechanical origin. It is highly probable that the influence on the capillary walls of the toxic state of the blood is a contributory cause. It is possible also that chronic peritonitis (see Vol. III. p. 943) has some share in its production, but it must be admitted that repeated tappings may be necessary in cases in which little or no peritoneal change is found after death. (*Vide* also art. "Oedema," p. 510.)

Jaundice is ordinarily absent throughout the entire illness, there being nothing more than a yellowness of the conjunctivae, and a sallow, icteroid complexion. If present it is usually slight, and it may subside and disappear, being probably catarrhal in origin. The urine is often diminished in amount, and presents abundance of urates and sometimes bile pigment. The amount of urobilin is increased. Urea is diminished in a late stage, while uric acid is increased. Glycosuria in common cirrhosis is a rare occurrence, but in so-called bronzed diabetes the cirrhosis with pigmentation of the skin is generally accompanied by glycosuria. Albuminuria, if present, is generally due to coincident disease of the kidneys. In a late stage a secondary anaemia comes on. Oedema of the feet and shins becomes marked, and may extend up on to the abdominal wall.

Often in a late stage there may be effusion of fluid into one or both pleurae ; this may be of simple origin, but often it is found to be due to a tuberculous pleurisy. As a rule there is no fever in this form of

cirrhosis ; but if a patient be under continual observation for a long period, we may often observe an occasional rise of two or three degrees for a few successive evenings, or even for longer periods.

The distended capillaries on the cheeks, the so-called venous stigmata, which are attributable to alcoholic excess, are commonly visible in cirrhosis at a very early period. By the time that ascites has arisen the face has usually altered and has begun to assume a very characteristic appearance. It is thin and wasted, and the malar bones are prominent ; the eyes are somewhat sunken ; the conjunctivae are yellowish, and the complexion is sallow and unhealthy. The process of digestion is impaired, and absorption of nutritive material from the intestinal canal is diminished, so that there is a progressive loss of bodily strength with emaciation. The trunk and extremities are ill-nourished, and at a late stage the attenuated frame offers a marked contrast to the swollen abdomen.

The spleen may sometimes be felt, but in most cases it is obscured by ascites or tympanites.

The liver may often be felt below the ribs, and its edge may project downwards for one or two inches, so that its hardness, and possibly its nodular character, may be recognised. More commonly, however, it is masked by the ascites ; though even then it may often be felt by a sudden dipping movement of the hand, which displaces the overlying fluid. The recognition of a small liver is a matter of greater difficulty ; and generally speaking, considering the frequent flatulent distension of the bowels, not much stress can be laid on a resonant note at the right costal margin. Attacks of pain over the liver, and more frequently over the spleen, may occur from time to time, and these are doubtless to be attributed to attacks of local peritonitis. Tympanites is often a troublesome symptom, which may materially add to the gravity of a case by the production of collapse of the bases of the lungs.

As the illness wears on, with progressive emaciation and increasing feebleness of voluntary and cardiac muscle, the patient is apt to shew signs of poisoning, which are probably attributable to the increasing interference with the function of the liver. He becomes liable to epistaxis, to bleeding from the gums, and to purpuric eruptions on the trunk and extremities. Large haemorrhages may occur into the abdominal wall, and occasionally into the subperitoneal tissue. Uncontrollable diarrhoea is also a common event, as in uraemia. Digestion is at a standstill, and he may thus sink from sheer asthenia, or may be hurried off by pulmonary inflammation. Often for some time before the end his mind may wander at night, perhaps also in the daytime. Occasionally a noisy delirium sets in; but more commonly the end is ushered in by apathy and increasing feebleness of body and mind, passing into drowsiness, coma, and death.

Portal cirrhosis in children does not differ materially from the disease of adults. Perhaps pyrexia is more common. There may be great difficulty in distinguishing it from tuberculous peritonitis, with ascites as the chief feature (see Vol. III. p. 957).

Complications.—In view of the general effect of alcoholism in lowering resistance to bacterial disease, it is intelligible that alcoholic cirrhosis should often be accompanied by tuberculosis, and this secondary infection may hasten the end. It is reckoned that the lungs are infected in 22 per cent, and the peritoneum in 9 per cent of those dying from cirrhosis. Pleurisy with effusion is not uncommon, and this is often tuberculous in origin. It is perhaps more frequent on the right side than the left. The fluid is usually serous or sero-fibrinous, but it is often tinged with blood. Other affections due to alcoholic excess, such as delirium tremens, chronic alcoholic insanity, and peripheral neuritis, may coexist. Occasionally the symptoms of chronic renal disease are added to those of cirrhosis. Thrombosis of the portal vein is a rare complication, which is followed by the rapid development of ascites, and adds materially to the gravity of the illness (*vide p. 142*). A terminal infection of the peritoneum leading to a suppurative or fibrinous peritonitis is not uncommon, but as it occurs when the patient is nearing the end it is not always recognised during life.

Course and Prognosis.—From the obscurity of the early stages of the disease no accurate estimate of its total duration can be given. Certainly two or three years from its first recognition may elapse before death occurs. Occasionally acute cases are seen which apparently run their full course in a few months. Death is generally due to the toxæmia, malnutrition, and cardiac failure, seldom to haematemesis. In the remaining cases it is due to intercurrent disease, tuberculosis, or a terminal peritonitis.

Though the morbid process and its symptoms may remain stationary for a long period if the patient come under treatment at an early stage, any such improvement to which the term "recovery" can be applied is extremely rare, and the possibility of erroneous diagnosis at once crops up in all such cases. In one recorded case, however, in which the diagnosis was confirmed by the supervention on separate occasions of mental symptoms and of peripheral neuritis, both clearly of alcoholic origin, the patient was in good health after repeated tappings, the first of which was performed some six years before (Bristowe). In another instance the patient was in good health after fourteen tappings, the first of which was more than three years before (Bristowe). A striking example is afforded by the case of a patient who died with contracted granular kidneys and pericarditis in St. Thomas's Hospital. Twelve years before he had been under the care of Murchison in the same hospital for alcoholic cirrhosis and ascites. From that date the patient, who had previously drunk freely, became a teetotaller, and during those twelve years he had been in fair health. At the autopsy the liver was found to weigh 59 oz., its capsule was much thickened and adherent to the diaphragm, the cut surface was that of a hobnailed liver, and the microscope revealed the usual appearance of multilobular cirrhosis.

The essential conditions for improvement or recovery in any degree are a restoration of the functions of the liver by compensatory hyper-

plasia of the cellular elements and the establishment of free communication between the portal and general systemic veins.

Diagnosis.—In an early stage, when the symptoms are mainly those of gastro-intestinal disturbance in an alcoholic subject, portal cirrhosis is more readily suspected than certified, but the suspicion, even if it is erroneous and premature, is probably of benefit to the patient. The clinical features and natural course of the disease, with the occurrence of haematemesis, or ascites, or both, are so well defined that mistakes should be rare. But in all cases in which the history of alcoholic excess is not well marked and the condition departs in any particular from the natural course, the diagnosis must be slowly reached and the mind must be open to the possibility of other disease. Haematemesis may occur when previous gastric symptoms have been slight or of short duration and alcoholic excess is a matter of doubt. It may then be for a time impossible to distinguish between cirrhosis and a duodenal ulcer, unless such physical signs as enlargement of liver or spleen and dilatation of abdominal veins are forthcoming. Points of distinction must be sought in the greater liability to pain in association with duodenal ulcer, its characteristic relation to the taking of food, and its situation; and these points may be contrasted with the catarrhal gastric and intestinal symptoms of cirrhosis. The difficulty is less likely to occur as regards a gastric ulcer. In rare cases vomiting of red blood is an early occurrence in carcinoma of the stomach at a time when there are no physical signs and no failure of health or nutrition. An examination of the stomach contents after a test-meal may be of service. The haematemesis of splenic anaemia and Banti's disease (see Vol. V.) must also be borne in mind, and examination of the blood will throw light on the case.

Similarly ascites may appear when with an absence of physical signs the preceding history and symptoms are not strong enough to bear a conclusion. Tuberculous peritonitis, especially in children, is sometimes a source of difficulty, and cases occur in which a diagnosis can only be made by examination of the fluid. This has a higher specific gravity, and contains more protein than the fluid effusion of cirrhosis, and the cytology of the fluid will often afford additional evidence. In uncomplicated cirrhosis the ascitic fluid shews a preponderance of endothelial cells (Cade, Ross); in tuberculous peritonitis of lymphocytes, and in ordinary inflammation of polymorphonuclear leucocytes. In such doubtful cases it is possible to empty the abdominal cavity by an incision which can serve for the Talma-Morison operation if necessary. In adults the most important difficulty arises in connexion with syphilis (see p. 201). A chronic peritonitis (see p. 167) may be indistinguishable from cirrhosis, and the diagnosis must rest on the greater duration of life after the first tapping in the former disease, and on the absence of indubitable signs of cirrhosis. The character of the fluid may also be of use. Carcinoma may arise in an abdominal organ, and by quick dissemination over the peritoneum may present an illness of which ascites is the prominent feature, whilst indications as to its cause are scanty. The colon and ovary are the most

common sites of the growth in such cases. Difficulty is less common in connexion with carcinoma of the pancreas and the stomach, inasmuch as in both cases (in the former by direct pressure and in the latter by secondary growth in the liver) jaundice is generally associated with the ascites, a combination which is rare in cirrhosis. Ovarian papilloma may come under observation at a time when ascites is the only obvious condition. A simple ovarian cyst may be productive of ascites, and a pelvic examination should always be made. It is possible that ascites may arise from the presence of enlarged glands in the portal fissure. Hydatid on the under surface of the liver with recurring ascites has been mistaken for cirrhosis. The condition of enlargement of the liver with ascites due to cardiac disease and backward pressure may occasionally bear some resemblance to cirrhosis. This is most likely to occur when the cardiac condition is one of pericardial adhesion (especially in children), and the doubt is hardly possible in connexion with valvular disease. Sometimes when cirrhosis and chronic renal disease are associated, the signs and symptoms of the latter may so predominate that the condition of the liver is not recognised during life. Finally, when neither haematemesis nor ascites has occurred, difficulty of diagnosis may arise in cases in which a moderate enlargement of the liver is the chief feature, and such conditions as chronic malaria, lardaceous disease, leukaemia, and Banti's disease must be borne in mind. More important and difficult is the distinction between cirrhosis and syphilitic disease of the liver (see p. 201). Primary carcinoma of the liver, in the absence of jaundice, can hardly be distinguished from cirrhosis. For the diagnosis between cirrhosis and secondary malignant disease of the liver, see p. 212.

Treatment.—Efficient treatment depends on early diagnosis. Alcohol in any form, dietetic or medicinal, must be absolutely prohibited, though in late and hopeless stages of the disease occasions arise when its use is necessary. All spices and irritants must be excluded. The diet must be plain and simple; it should be ample for the maintenance of strength, while excess must be carefully avoided. At the beginning of treatment milk should form the main, if not the only article in it. From three and a half to four pints a day may be given to an adult, in various ways, according to taste; slightly diluted with some alkaline water, or as a jelly, or in the form of a milk soup containing some vegetables. It is well to avoid meat entirely for a time, or at any rate to allow only white meat or fish in small quantities. All meat broths and soups may well be discarded, unless their temporary stimulant effect be required. Vegetables and fruit may be allowed, those kinds being preferred which contain least starch. And, as a general rule, it is well to reduce all forms of starchy and saccharine food to a minimum, in view of the state of the stomach and the proneness of these substances to undergo fermentation. If possible, complete rest and plenty of fresh air should be secured for these patients.

No drug is known which can either retard or remove the fibrosis, or promote compensatory hyperplasia of liver-cells. An extract

of liver is on trial, but its effect is uncertain. Iodide of potassium should always be employed in full doses, if there is any suspicion that the disease may be, even in part, of syphilitic origin.

For the rest, the treatment is symptomatic. According to the prevailing symptoms there may be used mineral acids, strychnine, and bitter tonics, or preparations of bismuth with bicarbonate of sodium and a few drops of liq. morphinae or dilute hydrocyanic acid, or gastro-intestinal antiseptics, such as creosote, thymol, salol, and salicylate of bismuth. Constipation requires the use of saline aperients such as Carlsbad salts, Apenta, and the like. In some cases calomel may be used with advantage. Diarrhoea is apt to be intractable. Although the attendant loss of fluid from the portal area is at any rate not harmful, yet the passage of the contents of the bowel is at the same time so hurried that absorption of nutritive food-products is imperfect. Gastric digestion and absorption being already at a low ebb, this diarrhoea has a disastrous effect, and in many instances it is the beginning of the end. The subnitrate or salicylate of bismuth in large doses is perhaps the most efficient means of coping with it ; the mineral acids, catechu, and the strong preparations of iron, such as the pernitrate, may also be tried ; but opium is seldom safe at this stage of the disease. In many cases all treatment fails to check it.

The occurrence of haematemesis, however slight, must be taken as the signal for absolute rest of the body as a whole, and especially of the stomach and adjacent part of the oesophagus. All food and fluid (including ice) by the mouth must be forbidden, and, at any rate during the few days of danger, the patient must be kept entirely on rectal feeding. It is extremely doubtful whether ergot or ergotin is of any avail ; the use of nitrite of amyl has been suggested on definite grounds. But opium, preferably as the hypodermic injection of morphine, is certainly of indirect value in calming the patient and allaying his anxiety. Adrenalin given by the mouth to produce its local effect seems to be of value. If the haemorrhage lead to dangerous collapse, infusion with normal saline solution subcutaneously, or into a vein, should be adopted.

Such a degree of ascites as will distend the abdomen and exercise pressure on the diaphragm, is at once a danger and requires removal. There is no doubt that diuretics, such as digitalis, squill, copaiba, and diuretin, do in some instances ensure the passage of an increased amount of urine, even so far as to promote a perceptible diminution of the ascites. Though such a treatment is probably harmless, it is too often useless, especially in cases of extreme ascites in which the diminished excretion of urine is attributable to pressure on the renal veins. Perhaps the most satisfactory diuretic to be used in such a case is the well-known combination of mercury, digitalis, and squill. The propriety of attempting to remove ascitic fluid by powerful purgatives is still more questionable. It is, of course, well to ensure free daily evacuation of the bowels by the matutinal use of saline aperients, but anything more drastic than

this is certainly not to be recommended. In fact, experience has shewn that paracentesis is the wisest course, and it should undoubtedly be employed at an early stage, and not be postponed until upward pressure upon heart and lungs is already severe. In all cases the suitability of the patient for surgical treatment by the Talmage-Morison operation should be considered. The operation consists in the establishment of adhesions by scraping and suturing between liver, omentum, and abdominal wall. It was founded on the view that ascites is due to increased portal pressure, and it has for its object the production of relief-anastomoses with the general systemic veins, over and above the anastomoses so commonly opened up by nature. The success of the operation in some cases is most striking. Those who believe that the ascites of cirrhosis is purely the result of toxæmia, or of a chronic peritonitis, are unable to explain the benefit which is thus afforded. The success is intelligible, however, if it is allowed that whilst ascites is partly a toxic phenomenon, it is largely also dependent on increased portal pressure. Not only may a recurring ascites be prevented by the operation, but great improvement of the general health may ensue, and it is reasonable to attribute this improvement to the diminution of the venous congestion of stomach, intestine, and spleen. It is impossible to estimate the results from statistics, successes being more readily reported than failures. Greenough's figures give 57 per cent of deaths and failures, and 42 per cent of success in some degree, nine of these being living and in improved health two years later. A summary of continental results by Mr. Sinclair White gives deaths 33 per cent, failures 15 per cent, improved 13 per cent, and cured 37 per cent. As regards these deaths and failures, it must be remembered that the operation was at first undertaken in late stages when death was in sight, and even in these it is seldom that the end is apparently hastened. Cirrhotic patients are bad subjects for operation, and it is clear that cases must be carefully selected. The necessary conditions suggested by Dr. Drummond and Mr. Morison are that there should be no cardiac, pulmonary, or renal complication, and that the patient should have survived one or two tappings. Rapid wasting, signs of toxæmia, and any degree of jaundice are adverse points. The risks lie in the supervention of peritoneal infection, erysipelas, intestinal obstruction, and, oddly enough, haematemesis. A case of pure alcoholic cirrhosis under my care was subjected to this operation in 1901 after six tappings. The operation shewed a small hobnailed liver with no sign of peritoneal change. He was tapped a seventh time three weeks after the operation, an eighth time two weeks later, and a ninth and last time four weeks later. In January 1908 he was in good health and in active work, presenting oedema of shins and an enlarged spleen as the only signs of disease.

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BILIARY CIRRHOSIS

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THE two forms of biliary cirrhosis, (I.) Hypertrophic biliary cirrhosis and (II.) Obstructive biliary cirrhosis, present distinctive clinical and pathological features, and will therefore be described separately.

I. HYPERSTROPHIC BILIARY CIRRHOSIS.—SYNOMYS : Hanot's cirrhosis ; Hanot's disease ; Biliary cirrhosis.

Definition.—A disease characterised, *clinically*, by its long duration, by the presence of chronic jaundice, enlargement of the liver and spleen, and intercurrent attacks of abdominal pain with pyrexia (crises), and by the absence of persistent ascites or signs of portal obstruction ; *histologically* by cholangitis and a cirrhosis primarily monolobular in type.

History.—A brief account of the steps which led up to the recognition of the distinctive features of the disease by Hanot in 1876 is not unnecessary, as some confusion still exists in this country as to the relation between biliary and multilobular cirrhosis. Until 1849 there had been considerable difference of opinion as to the relation between the large (so-called "hypertrophic") form of cirrhotic liver, and the small hobnailed variety. Carswell, and later Hallmann, and others, had proved that the essential pathological change in the cirrhotic liver described by Laennec in 1819 was the formation of fibrous tissue, but it

had been generally held that the large cirrhotic liver was but an early stage in the evolution of the small variety. In 1849 Requin shewed that the small cirrhotic liver was characterised by a high degree of atrophy of the liver-cells, whilst in two cases of large cirrhotic liver investigated by himself hypertrophy of the hepatic cells appeared to predominate. Hayem in 1874 described cases of "hypertrophic" cirrhosis as distinct from the "atrophic" form, in which the enlargement of the liver persisted throughout the course of the disease, and in the same year Cornil published an accurate and complete account of the histological changes in cases like those of Hayem's, which must be regarded as identical clinically with those subsequently known as hypertrophic biliary cirrhosis. But to Hanot must be given the credit of having been the first to recognise clearly the distinctive clinical features associated with the morbid characters described by Cornil, and his classical series of cases published in 1876 is the first distinct and complete account of biliary cirrhosis.

In recent years some writers in this country have expressed doubt as to the existence of this form of cirrhosis as a distinct variety. The explanation of this attitude may be ascribed to the undoubtedly great rarity of cases of Hanot's cirrhosis in Great Britain, and also to the tendency in the later stages of the disease to the association of a multilobular cirrhosis, thus producing what is known as the "mixed" form. Without a complete clinical history such cases may easily escape recognition; further reference will be made to this subsequently. Attention must be drawn here to the great confusion which has been caused by the misuse of the adjective hypertrophic as applied to cirrhosis without any qualifying word such as biliary. Dr. Rolleston rightly lays great stress on this point, and urges that the designation hypertrophic cirrhosis should be entirely given up on the grounds that it is so often loosely applied to any form of cirrhotic liver in which there is great hepatic enlargement.

Etiology.—*Ser.*—In adult life males are undoubtedly affected more often than females; in Schachmann's 26 cases there were as many as 22 males to 4 females. In the juvenile type in a series of 7 cases, Gilbert and Fournier found 4 boys and 3 girls affected, and I have collected 15 other cases, making a total of 22, and of these 13 were male and 9 female children.

Age.—The disease is commonest between the ages of 20 and 35, and is rare after 40, thus contrasting, as Dr. Rolleston points out, with multilobular cirrhosis, in which the average age is about 48 years.

Race and Climate.—It is difficult to draw any exact conclusions as to the importance of these factors. The majority of the published cases have occurred on the continent of Europe, and in Great Britain the disease is undoubtedly extremely rare. In Mexico a form of cirrhosis has been described (Carmono y Valle) attended by hepatic enlargement and jaundice, which differs from Hanot's cirrhosis in the absence of splenic enlargement and in its much shorter course, and is probably a distinct

endemic form of disease. The same may be said of the cirrhosis prevalent amongst native infants in India described by M'Nally, Gibbons, and Ghose, which resembles in some respects biliary cirrhosis. These conditions are probably quite local in their incidence and may eventually prove to be due to some specific cause. In the Hindu form the disease begins as a pericellular cirrhosis, and unsuitable food and bad hygienic conditions appear to be the chief factors in its production.

There is reason to believe that *heredity* may be a factor in the causation of the disease ; thus, Dreschfeld described the disease in two brothers, and Hasenclever in three cases, two sisters and one brother. A family tendency to chronic jaundice and enlargement of the liver and the spleen undoubtedly exists, as shewn by the recorded groups of cases (Boinet, Barlow and Shaw, Osler), some of which have undoubtedly been examples of Hanot's disease. The "family" form of the disease is further referred to on p. 192.

A history of *alcoholic excess* is present in a small proportion of published cases, but there is no evidence that it has any special influence beyond rendering the liver more liable to the action of infective or toxic agents. As Dr. Rolleston points out, the extreme rarity of biliary cirrhosis in this country where alcoholism is so common practically excludes any important relation between them.

Syphilis plays as unimportant a part in the causation of Hanot's disease as it does in multilobular cirrhosis. Hanot, and also Marçais, have described a form of syphilitic hepatitis with enlargement of the liver and chronic jaundice which differs from biliary cirrhosis both clinically and pathologically.

Specific Fevers.—A certain number of cases have been recorded which appear to have directly followed an infective fever, such as scarlet fever (F. Taylor), though post-scarlatinal cirrhosis in children is usually a special form and not a true biliary cirrhosis (Bingel, Gilbert and Lereboullet).

Enteric Fever.—A large group of previously published cases has been collected by Odon in which biliary cirrhosis followed enteric fever. The exact nature of many of these cases appears doubtful in the absence of autopsies, and there is not sufficient evidence that these cases were due to the *Bacillus typhosus*, as the agglutination test was obtained in one case only.

Malaria does not appear to play any part in the etiology of the disease, though a history of paludism has been present in a few cases.

Other Bacterial Infections.—Staphylococci and streptococci (Osler), the colon bacillus (Gilbert and Fournier), and *Diplococcus pneumoniae* (Hayem) have been found in cases of Hanot's cirrhosis ; but no definite conclusion can be drawn as to the importance of these observations, as it is difficult to exclude the probability that they were secondary or terminal infections.

Poisons.—Although we are driven to the conclusion that the disease is due to some toxin, which is conveyed to the liver by the blood and

provokes a descending cholangitis, no such substance has been found. Many experiments have been performed with numerous toxic bodies, but with practically negative results.

Morbid Anatomy.—The *liver* is usually greatly enlarged and may weigh as much as 6 lbs. $11\frac{1}{2}$ oz. (= 3053 grms.) (Osler's case). The surface is usually smooth, though in some cases small white granulations may be visible, and perihepatitis with localised adhesions is not uncommon. On section the liver substance is firm; its colour varies from deep yellow to dark olive-green, the latter being the more characteristic. Sometimes small white or pale yellow granulations may be visible to the naked eye. In one case in a child, which I examined, these were extremely distinct and resembled grey miliary tubercles scattered uniformly throughout the organ. The intrahepatic ducts shew no change to the naked eye. The gall-bladder and large bile-ducts may contain viscid bile, but are otherwise normal.

The *spleen* is enlarged to a varying degree and is sometimes huge in size, and its enlargement may be relatively greater than that of the liver. Perisplenic adhesions are often present, but the capsule rarely shews a degree of thickening comparable to that found in portal cirrhosis. The substance is firm but presents no characteristic appearance.

Lymphatic Glands.—Enlargement of the abdominal lymphatic glands may occur, and sometimes the glands at the hilum of the liver are affected. It has been suggested that the jaundice may be caused by pressure exerted by these glands on the extrahepatic bile-ducts, but it is improbable that this can be an important factor, since in the majority of complete cases no such enlargement has been observed.

Stomach and Intestines.—Hanot laid special stress on the freedom of these organs from morbid change, catarrhal conditions such as gastritis and duodenitis being usually absent.

Peritoneum.—Localised perihepatic adhesions are found in a certain number of cases. In typical (not "mixed" cases) the peritoneum does not exhibit the opacity and thickening so common in multilobular cirrhosis. A small quantity of ascitic fluid is usually found after death.

Vascular System.—There are no signs of chronic portal obstruction, such as distension of the oesophageal or abdominal veins.

Histology.—The characteristic feature of the disease is a mono- or inter-lobular cirrhosis, the "insular" form of Charcot and Gombault. Bands of rather delicate connective-tissue fibres separate individual lobules, thus presenting a marked contrast to the coarser and denser arrangement found in the multilobular or portal (alcoholic) variety. The fibrosis is not confined to the interlobular regions but can be traced as fine fibrillae invading the outer zone of the lobules and passing between the hepatic cells. Elastic fibres are present in the fibrous tissue, but not to the same extent as in multilobular cirrhosis (Carnot and Amet). A prominent feature is the presence of small tubules or columns of cells, the pseudo-biliary canalicular, with sinuous courses anastomosing freely in the connective tissue. They consist of small cubical cells with a small

amount of clear protoplasm surrounding a large deeply staining nucleus. In some places the cells are arranged in a double row with a definite space intervening, which may contain bile pigment and thus closely resemble small bile-ducts ; or, again, the cells are arranged in single file as columns separated from each other by fibrous tissue. These cannot be regarded as peculiar to this form of cirrhosis, as they occur with fair frequency in multilobular cirrhosis and also in syphilitic lesions. Originally they were looked upon as newly formed bile-ducts, but for want of evidence this opinion is untenable. Hanot considered that they are the result of proliferation of the liver-cells—an opinion supported later by Dreschfeld. Dr. Findlay regards these pseudo bile-ducts as a reversion to the embryonic type of liver brought about by an attempt at regeneration and to the formation of a compound tubular gland on the part of the surviving liver-cells. A monolobular cirrhosis is characteristic of the disease, but in a certain proportion of cases, especially those of long duration, a considerable degree of fibrosis may be found in the portal spaces. Cases of this kind shewing portal combined with monolobular cirrhosis must be regarded as belonging to the "mixed" type previously referred to, in which fibrosis of portal origin has been added to one arising in connexion with the biliary radicals. The liver-cells may shew comparatively little change. Hanot regarded this as a feature in the disease, and described genuine hypertrophy of these cells and gave this as an explanation of the increased size of the liver. Degenerative changes are certainly less prominent in biliary cirrhosis than in portal cirrhosis, but too much weight should not be attached to this distinction, as in late cases the liver-cells are often greatly altered. The biliary capillaries and the smaller bile-ducts present very characteristic appearances. The epithelial lining has undergone proliferation and the lumen is blocked or reduced in size by an increase in the number of cells lining it, by desquamated cells, and by plugs of inspissated bile. The larger bile-ducts, on the other hand, shew little or no change. These evidences of an inflammatory process affecting the biliary capillaries and smaller ducts afford a sharp distinction between biliary and portal cirrhosis, as they do not occur in the latter form with anything approaching the same degree of frequency. The blood-vessels shew little or no change, even the smallest capillaries remain patent (Ackermann). Pigment injected into the portal circulation readily makes its way into the hepatic veins.

The *spleen* shews diffuse fibrosis with some increase in size of the Malpighian bodies (lymphatic hyperplasia), or these structures may have undergone fibrotic atrophy.

The *pancreas* is rarely enlarged and shews no naked-eye change, though microscopically there is often some slight degree of fibrosis around the ducts (Lefas).

Pathology.—The clinical course of the disease and the histological changes in the liver support Hanot's opinion that the primary and essential change in hypertrophic biliary cirrhosis is catarrhal inflammation of the biliary capillaries. The cause of this cholangitis remains at

present obscure. Bacteriological investigations have hitherto given varying or negative results, but it is impossible to exclude bacterial infection as the cause. The changes found in the biliary capillaries closely resemble those set up by toluylenediamine, and it would seem probable that they are produced by some toxin, but whether of bacterial origin or not it is impossible to say. The general consensus of opinion at the present time favours the view that the cholangitis is due to an infection—a conclusion strongly supported by the clinical features of the disease, such as crises with accompanying fever and leucocytosis, enlargement of the spleen and lymphatic glands, and the occasional occurrence of peritonitis. The jaundice is the direct result of the cholangitis which leads to blocking of the capillaries and smaller bile-ducts. The bile itself is unduly viscid, and deposition of pigment granules is common in the obstructed ducts and canaliculi. The fibrotic changes must be regarded as secondary to the morbid process in the biliary capillaries. This explanation is supported by the comparatively slight degree of fibrosis seen in the early stages of the disease, and also by the monolobular distribution of the newly formed fibrous tissue which not uncommonly extends some little way into the outer portions of the lobules.

The question naturally arises, by what route the infection or irritant reaches the bile-ducts and sets up cholangitis. Two answers have been given to this. The first, advanced by a number of French writers (Gilbert and Surmont, Chauffard), is that the primary cause of the condition is an *ascending infection* of the bile-ducts, the infection being derived from the intestine and producing an ascending cholangitis. The alternative hypothesis is that the irritant which reaches the liver by the general blood-supply, induces in the smaller bile-ducts and capillaries inflammatory changes resembling those set up by toluylenediamine, in other words, that it is a *descending cholangitis* (Rolleston). This would seem to be much the better explanation of the two. The absence of inflammatory changes in the duodenum and in the extrahepatic and the larger intrahepatic bile-ducts would, in the great majority of cases, exclude the possibility that the biliary capillaries have become infected by this route, or in other words, that an ascending cholangitis has occurred. In cases of Hanot's cirrhosis the larger bile-ducts shew no evidence either of inflammatory processes or of obstruction, though occasionally soft friable masses of cholesterol may be found in the gall-bladder. Further, though the pancreas may shew some degree of fibrosis in biliary cirrhosis, no increase of size results as would be expected if the cause were a chronic infection ascending from the duodenum. Lastly, as Dr. Rolleston points out, "the fact that the spleen may be enlarged before the liver and before there is any jaundice, which may be regarded as evidence of infection of the bile-ducts, is against the theory of an ascending infection and is in favour of the primary factor being a general haemic infection."

Symptoms and Course.—The onset of the disease is usually attended by slight jaundice accompanied by general malaise, headache, anorexia,

dyspepsia, and increasing weakness. In a certain proportion of cases gastro-intestinal symptoms, such as nausea or vomiting with diarrhoea, are prominent. A sensation of weight or dragging and sometimes acute pain is felt in the abdomen. The jaundice is usually slight, though it may vary considerably in intensity during the course of the disease. There may be a faint yellow tint of the conjunctiva only, or the skin may become bright yellow. The dark olive-green complexion of chronic obstructive jaundice is rare in biliary cirrhosis, even in its later stages. During this early period there is considerable uniform enlargement and tenderness of the liver, its surface being smooth and moderately firm. The spleen may be enlarged coincidentally and sometimes to a greater degree than the liver. There is no ascites. The temperature is usually slightly raised. The urine contains bile, while the stools retain their colour, shewing that bile passes into the intestine. In the course of a few days, or at most two to four weeks, these early symptoms, with the exception of the jaundice, may entirely disappear, and the patient apparently regains his normal health. The jaundice and the enlargement of the liver and spleen, however, persist throughout the course of the disease.

One of the most characteristic features in the further progress of the disease is the periodic occurrence of exacerbations attended by pain, often very acute, in the hepatic region, by pyrexia and increase in the jaundice. The liver and spleen become larger and tender and the urine contains more bile. Occasionally a small amount of free fluid can be detected in the abdominal cavity during these attacks, but its presence is merely transient. These exacerbations, or "crises," as Hanot, who laid great stress on them, called them, are of short duration, and the pain gradually subsides though the liver remains larger after each attack. Hanot ascribed the pain and transient ascites to the presence of peri-hepatitis, and in support of this stated that the surface of the liver may feel rough during the attacks. This explanation has not been confirmed, and it is more probable that the pain is due to an increase in the cholangitis. In the intervals between the crises the patient often feels comparatively well; except for the persistent jaundice and at times a dragging feeling in the hepatic region, he complains of little or nothing, and his bodily strength and general condition are generally well maintained. In some cases a permanent brown pigmentation of the skin, especially of the hands and fingers, is present (Fournier, F. Taylor). This state of things usually lasts for four or five and sometimes even twelve years (Goluboff). Though the termination is often long delayed, the disease is probably always fatal. The crises increase in frequency and eventually abdominal pain and pyrexia become constant. Cutaneous, gastric, and intestinal haemorrhages may occur, and ascites may develop as a terminal event. The patient gradually sinks into a drowsy condition which passes into coma, the final state closely resembling that of *icterus gravis*.

Blood Changes.—No characteristic blood changes have been found at

any period of the disease. There is usually some diminution in the number of erythrocytes and in the amount of haemoglobin, while a moderate degree of leucocytosis is generally present and becomes higher as symptoms of toxæmia become more marked. Hayem recorded an isolated observation of a case in which, during the last week of life, there was an intense anaæmia with a colour-index of 1.27 to 1.46 and a leucocytosis of 15,500 to 21,800 (Cabot).

The urine shews little or no change beyond the presence of a varying amount of bile pigment and occasionally of urobilin. Polyuria often occurs (Milian). Albumin may be present in small amount during the febrile periods. The excretion of urea undergoes no notable change.

The preceding account of the clinical features of the disease follows closely that given by Hanot, but it should be borne in mind that cases occur which differ in some particulars from this typical form, and have given rise to considerable controversy. The enlargement of the spleen may precede and may be relatively greater than that of the liver, and certain French writers (Chauffard, Gilbert and others) have urged the division of these cases into separate groups under such titles as hyper-, meta-, para-splenomegalic forms, a nomenclature which would appear to be not only cumbrous but also unnecessary. A far more important variation is the "mixed" type which is not infrequently met with, especially in the later stages of the disease. In this form a portal cirrhosis has supervened on the biliary cirrhosis, so that ascites and enlarged abdominal veins result, and the final picture may closely resemble that of a portal or multilobular cirrhosis.

Juvenile Form.—Special reference must be made to the form met with in children as described by Gilbert and Fournier, F. Taylor, and others. The course is more rapid than in adults, and is sometimes attended by clubbing of the fingers, deformity of the nails, and thickening of the bones about the wrists and ankle-joints (osteo-arthropathy). Clubbing of the fingers may exceptionally be met with in other forms of hepatic disease, such as obstruction to the bile-ducks and portal cirrhosis (Rolleston). Effusions into the knee-joints may occur. Bodily development is retarded so that the patient may shew infantilism (*vide p. 486*) with delay or absence of the signs of puberty. There may be a diffuse brownish pigmentation of the skin resembling Addison's disease, or, in some cases, the hands and fingers are the only pigmented parts.

Family Form.—There are numerous recorded instances of several members of one family presenting a condition more or less allied to biliary cirrhosis (Boinet, Lereboullet, Osler, C. Wilson, Odon, Barlow and Shaw, Parkes Weber). In this form the duration of the disease is often greatly prolonged. The clinical features may shew distinct variations in members of the same family; thus, one member may suffer from biliary cirrhosis of the classical type, whilst others may have chronic jaundice with or without enlargement of the liver or spleen. It

has been suggested with considerable probability that some of these incomplete forms may be transitional between splenic anaemia and hypertrophic biliary cirrhosis (Rolleston). Several cases of the family form have been recorded as occurring after enteric fever; Odon has collected a number of instances of this association. Gilbert and Lereboullet suggest that there may be a family disposition to biliary cirrhosis, and employ the term "*cholémie familiale*" to express it. Dr. Parkes Weber's hypothesis that an individual tendency or a special "tissue proclivity" plays a part in the development of biliary cirrhosis appears to be specially applicable to the family form of the disease.

Diagnosis.—This should not present any great difficulty in a characteristic case. Jaundice, lasting for a long period without acholic stools, the occurrence of crises, and progressive enlargement of the liver and spleen present a sharply marked clinical picture.

From *portal cirrhosis* it can be distinguished by the absence of ascites, of distended abdominal veins, and of haematemesis at an early stage in the disease. The persistent jaundice met with in Hanot's cirrhosis is most unusual in portal cirrhosis. The diagnosis in the "mixed" form of the disease may be difficult, but in most instances the history that the chronic jaundice began early in the course of the disease should furnish grounds for regarding the condition as having most probably begun as a biliary cirrhosis. In *cholelithiasis* the jaundice is usually deeper, the hepatic enlargement is less, and the spleen is little, if at all, increased in size, and from obstruction of the common bile-duct there may for a time be acholic stools. Attacks of biliary colic, if slight, may resemble the crises occurring in Hanot's cirrhosis, but the agonising pain associated with gall-stones is very different from the hepatic pain associated with the crises. *Malignant disease* of the liver, whether primary or secondary, should not present any great difficulty in the differential diagnosis; the short course, great wasting, and frequent occurrence of complete obstructive jaundice in this condition are characteristic of new growth. In *splenic anaemia* the presence of a leucopenia and a greatly enlarged spleen, and the absence of crises and jaundice, usually distinguish it from biliary cirrhosis; some cases of Hanot's disease, however, present great splenic and comparatively little hepatic enlargement (the splenomegalic form), and may thus be difficult to diagnose. In *hydatid of the liver* the hepatic enlargement is usually not uniform, the spleen is not enlarged, and chronic jaundice is very rare. *Enlargement of the liver of gastro-intestinal origin* was described by Budd, and later by Hanot as Budd's cirrhosis; it is a chronic condition due to intestinal intoxication, and is characterised by great enlargement of the liver. There is, however, no jaundice and no splenic enlargement. Hanot, and more recently Marçais, described a diffuse form of hepatitis associated with *syphilis* which gives rise to enlargement of the liver and occasionally of the spleen, and to chronic jaundice. The duration of these cases is much shorter than Hanot's cirrhosis. The more ordinary forms of acquired syphilitic disease of the liver are fairly easily recog-

nised by the irregular shape of the liver and evidence of lesions elsewhere; the congenital form sometimes presents more difficulty in the absence of a syphilitic history or of signs of the disease, and the diagnosis may ultimately depend on the effect of antisyphilitic treatment.

Prognosis.—This must be regarded as hopeless, as the disease is slowly progressive. The duration may be greatly prolonged, and in the more chronic cases the patient's general condition is often well maintained, and except during the crises suffering may be quite slight.

Treatment.—The patient should lead a quiet life, in general healthy conditions, with very carefully regulated exercise. Confinement is unnecessary except during the crises, when he should keep in bed. Great care must be taken to avoid fatigue or exposure to cold, as neglect of these precautions may precipitate a crisis. The diet should be simple, easily digestible, and free from any stimulating articles such as condiments, curries, rich sauces. As the digestion is usually good, food should be nourishing and fairly abundant. During the crises it is advisable to keep the patient on an exclusively milk diet. Periodical visits to one of the health resorts, such as Carlsbad, Harrogate, Homburg, or Vichy, often prove of advantage.

As regards treatment by drugs, care should be taken to ensure an adequate and regular action of the bowels. Saline draughts, such as Condal water or Hunyadi Janos, are especially suitable. If the stools are unhealthy, and especially if offensive, salol or β -naphthol may be given with advantage. Calomel is the only drug which appears to have any beneficial action on the disease. Its use in repeated doses of one grain (0.06 gram) was first suggested by Sacharjin in 1885, and has since been warmly advocated (Sior, Goluboff). It may also be given in doses of $\frac{1}{10}$ to $\frac{1}{2}$ grain every three hours for periods of three days, with clear intervals of three days, for a month or longer. Under its influence the jaundice is said to diminish greatly or even to disappear, the spleen to get smaller, and the urine to become free from bile.

Operative treatment was introduced in 1891 by Terrier in the form of drainage of the gall-bladder. Greenough advocates this procedure in cases in which symptomatic treatment has failed to give relief and evidence of infection is present. The condition was relieved by operation in 13 out of 17 collected cases surgically treated; of these 12 recovered, 1 improved, 2 shewed no improvement, and 2 died.

II. OBSTRUCTIVE BILIARY CIRRHOSIS.—At the present time we may regard it as established by experimental work that occlusion of the extrahepatic bile-ducts is followed by a certain amount of fibrosis in the liver. This conclusion has not been arrived at without considerable controversy, which may be said to have begun with Dr. Wickham Legg's (56) observation, published in 1873, that ligature of the common bile-duct leads to hepatic cirrhosis. for although Wyss in 1866 and Hayem in 1872 had published similar experimental results, they do not

appear to have attracted attention. Dr. Wickham Legg added clinical evidence in 1876 by recording the effect on the liver of occlusion of the ducts by an impacted gall-stone in one case, and from pressure by hydatid cysts in a second; in both cases cirrhosis of the liver was present (57). In 1876 Charcot and Gombault published cases of cirrhosis associated with obstruction of the ducts, and also the results of experimental ligature of the common bile-duct in rabbits, and these investigators were the first to raise the question, afterwards so long disputed, whether the cirrhosis is the result of the obstruction pure and simple or depends on the presence of an infective process which may result from the operation. Drs. Vaughan Harley and Barrett in 1898 conclusively shewed that cirrhosis follows occlusion of the duct, even when the operation is perfectly aseptic. They produced a monolobular cirrhosis, which was regarded as due to the irritating action of bile passing through the walls of the smaller bile-ducts by osmosis as a result of the increased pressure brought about by ligature of the duct.

Etiology.—Obstructive biliary cirrhosis may be caused by gall-stones, malignant disease implicating the bile-ducts, or by pressure on the ducts from without by tumours, hydatid cysts, or enlarged glands, though it should be pointed out that in many cases of complete occlusion of the common bile-duct, notably in malignant disease, cirrhosis may be absent. Congenital obliteration of the bile-ducts leads to, or is associated with, cirrhosis (*vide* page 103). In Ford's series of cases this was the most frequent cause of complete obstruction of the ducts.

Morbid Anatomy.—The liver is usually greatly enlarged, the surface may be moderately smooth, though more often it is irregular and sometimes even hobnailed. In the more chronic cases the liver is small and resembles the multilobular form. Perihepatitis with adhesions is frequently found. On section it has a dark olive-green colour and the bile-ducts are dilated and full of dark viscid bile. In long-standing cases the ducts distended with mucus may be visible on the surface, forming slightly raised eminences. The substance is firm and tough, though far less so than in portal cirrhosis.

Microscopically the fibrosis may closely resemble that found in Hanot's cirrhosis; there is an interlobular distribution of connective tissue which may extend to some extent into the lobules. In other cases the fibrosis is multilobular or portal. The small biliary ducts and capillaries shew the same inflammatory changes, but, on the other hand, the large ducts are dilated to a degree which does not occur in Hanot's form. Pseudo-bile canaliculi are often found in obstructive biliary as in other forms of cirrhosis, but according to Ford they present a peculiar wreath-like arrangement in the portal spaces which he considers may possibly form a histological feature characteristic of obstructive cirrhosis serving to differentiate it from other varieties of cirrhosis. Pigment granules are abundant in the bile channels.

The large bile-ducts are dilated and often, but not invariably, shew an increase of connective tissue around them. In some cases it is apparent

that direct infection has taken place from the intestine, and evidence of an acute inflammatory process with foci of suppuration may be present in or about their walls. Dr. Parkes Weber draws an apt comparison between obstructive biliary cirrhosis and chronic interstitial nephritis accompanying partial or complete obstruction to the outflow of urine. In both cases an ascending infection may supervene and be the final cause of death. In some cases of obstructive cirrhosis the large bile-ducts may shew little or no change, whilst the smaller ducts and bile capillaries present distinct evidence of a cholangitis. This may have been brought about by the action of toxic bodies which, conveyed to the liver by the portal vein, but not being stopped by that organ, may enter the general blood-supply and be again brought to the liver by the hepatic artery (Rolleston).

The *spleen* presents no characteristic change except in cases in which the cirrhosis is multilobular; it may then be moderately enlarged.

The *pancreas* shews more marked changes than are found in Hanot's cirrhosis, chronic interstitial pancreatitis being a common result of occlusion of the lower end of the common duct, especially by calculi.

Pathology.—It is fairly obvious that several factors, acting either separately or simultaneously, may be concerned in the production of the histological changes found in cases of obstructive biliary cirrhosis, and this probably accounts for the varying characters and extent of the resulting lesions. Drs. Vaughan Harley and Barrett's experiments have shewn that aseptic ligature of the ducts leads to fibrosis monolobular in distribution, and their explanation that it is due to the increased pressure of the retained bile may be sufficient. At the same time it is possible that altered intestinal conditions due to the absence of bile may lead to the production of toxic bodies which give rise to cirrhosis. Clinically it is not clear that obstruction by itself does produce cirrhosis: obstruction secondary to cancer of the pancreas produces dilatation of the ducts and atrophy of the liver-cells, but these changes are rarely accompanied by fibrosis. Dr. Rolleston has pointed out that "malignant disease of the pancreas with complete biliary obstruction is not a rare disease, but it is remarkable that it is hardly ever associated with cirrhosis of the liver"; it would be of value to have further investigation of this association. The inflammatory conditions observed in the large bile-ducts are more readily explained: they are due to microbial infection which has ascended the extrahepatic ducts and given rise to the pericholangitic fibrosis so often found in cases of cholelithiasis.

The clinical features of the disease are those characteristic of obstruction of the bile-ducts, deep jaundice with acholic stools. Wasting and loss of strength are usually rapid, and the patient finally sinks into a state of cholaemia and coma. If the obstruction be incomplete or intermittent, as in some cases of cholelithiasis, the colour of the faeces may vary from time to time. The course of the disease is much more rapid than in Hanot's cirrhosis, and the prognosis is worse.

In cases associated with cholelithiasis attacks of colic may sometimes simulate the crises in Hanot's disease, but the occurrence of bile-free stools, if only occasional, should facilitate the diagnosis. The moderate degree of splenic enlargement in the obstructive variety contrasts with the far greater hypertrophy in Hanot's disease. In protracted cases portal cirrhosis may supervene with its attendant signs of portal obstruction, ascites, venous dilatation, and haematemesis.

Treatment resolves itself into the treatment of the obstruction by surgical methods, as little else is likely to produce any improvement in the condition.

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H. M. F.

TUBERCULOSIS OF THE LIVER

By W. HALE WHITE, M.D., F.R.C.P.

ALTHOUGH there are several forms of tuberculosis of the liver, it is far from common. New-born guinea-pigs often shew tuberculosis of the liver, if the mother is tuberculous; but in most animals, including man, it is excessively rare to find tubercle bacilli in the fetus, even when they swarm in the mother. Tuberculosis of the human placenta is hardly ever seen, but it does occur. In the medical literature of twelve recent years, I was able to find six cases only of transmission from the human mother of tubercle bacilli. When it does occur the fetal liver is the organ most often affected; this is what might be expected, since the fetal blood is returned by the umbilical vein to the liver; indeed, in such cases tubercle bacilli have been found in the blood of the umbilical vein (Bar and Rénon). Sometimes in these very rare cases, tubercle bacilli are found in the fetal liver without any obvious changes in that organ, but in other instances the infection of the liver has lasted long enough to cause hepatic miliary tubercles.

In fatal cases of generalised tuberculosis the liver often shews miliary tubercles. The bacilli are conveyed to it by the portal vein when the focus is at its periphery, for example in tuberculous ulceration of the intestine; otherwise they are conveyed by the hepatic artery. The miliary tubercles may be seen under the hepatic peritoneum, or in the substance of the liver. They are often very numerous, exactly resemble miliary tubercles elsewhere, and do not give rise to any clinical symptoms.

Tuberculous caseous disease of the liver occurs, but is decidedly rare. Sometimes a number of small caseous areas which have broken down to form cavities are seen, and when this occurs the caseous material may be discharged into the bile-ducts, just as caseous material from the lungs is discharged into the bronchi. Sometimes bile passing into these cavities stains them green or yellow, or, if haemorrhage has taken place, they are red. The tubercle bacilli are in these cases conveyed to the liver by the portal vein. This condition is sometimes spoken of as tuberculous cholangitis or pericholangitis. Before these numerous caseating masses break down they may be mistaken for nodules of lymphadenoma or other forms of growth, such as the fatty multiple adenomas seen in cirrhosis.

I think confusion has sometimes occurred between tuberculosis and psorospermosis. This form of tuberculosis does not give rise to any clinical symptoms, as there is never damage to a sufficient number of ducts to cause jaundice. In other cases the caseous masses are large, and, speaking generally, the larger they are the fewer they are. These large masses are very rare, but I have examined at least one such case after death. If the caseous mass is large, it does not usually rupture into the biliary channels, probably because it is so large that it destroys them, hence these large caseous masses are rarely bile-stained. They are sometimes called "solitary tubercle" of the liver, but usually more than one is present in the same liver; a specimen in the Guy's Hospital Museum shews a triangular pale area in the right lobe of the liver, measuring three inches across its base, and consisting of hepatic tissue invaded by a speckled yellow deposit which is caseous and histologically tuberculous. The whole liver is studded with small tuberculous masses. This specimen suggests that some at least of the large caseous masses are due to coalescence of smaller ones, and it also forms a link between the cases with many small caseous nodules and those with large ones. There is another specimen in which there are only two tuberculous caseating masses, each a quarter of an inch in diameter; this specimen makes it probable that some at least of the larger caseous nodules are not due to coalescence of several smaller ones. There is another in which almost the whole of the left lobe of the liver has been converted into a tuberculous abscess. In very rare instances, such as the last, the case presents itself as one of hepatic tumour or abscess. Mr. Mayo Robson successfully drained such an abscess. These large caseous masses may be confused with a breaking-down gumma or actinomycosis of the liver (*vide* Vol. II. Part I. p. 328). They are so rare that they are hardly ever diagnosed, although they may be suspected if a tumour of the liver is found in a person very ill from tuberculosis, especially if it is at the periphery of the portal vein.

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W. H. W.

SYPHILIS OF THE LIVER

By HERBERT P. HAWKINS, M.D., F.R.C.P.

OF all the abdominal viscera the liver is most liable to syphilitic affections, both in acquired and in inherited disease.

(A) ACQUIRED SYPHILIS.—In the secondary stage jaundice occasionally appears at the same time as the common roseola. From this coincidence in point of time it may fairly be attributed to a specific catarrhal cholangitis analogous to the skin condition. Pressure of enlarged syphilitic glands in the portal fissure has been suggested as an alternative explanation. Although the first explanation is probably correct, it is possible that, in some cases at any rate, this cholangitis may be associated with a more severe though still curable lesion in such a pericellular infiltration as is known to occur in congenital syphilis. This is rendered the more probable by our knowledge that this syphilitic jaundice has in rare instances passed on into acute yellow atrophy (see p. 117). Clinically this jaundice can be differentiated from the ordinary catarrhal disease only by the presence of other signs of syphilis. Under mercurial treatment it rapidly disappears.

Of the tertiary stage, (1) the *syphiloma* or *gumma* is the chief lesion. This consists primarily of a mass of granulation tissue, sometimes containing giant-cells, which in its spreading shews active invasion of the surrounding liver tissue, entering lobules and isolating individual hepatic cells or groups of cells. The arterioles around it shew a syphilitic arteritis. But in the condition in which it is commonly observed some degree of caseation has taken place and a fibrous capsule has been developed. In a still later stage the mass shews nothing but caseous material, surrounded by a zone of new cicatricial tissue which has a degree of cellularity varying with its age; and from this zone fibrous bands may radiate for a short distance into the surrounding tissue. At the margin a few new-formed biliary canaliculi are commonly seen. The caseous gumma is a dead-white or greyish-white mass, roughly spherical. It may occur singly, but commonly there are many, varying in size from a pea to a tangerine orange, scattered here and there or fused together into a large lobulated mass. They may occur in any part of the liver, superficial or deep, but they are especially common at the junction of right and left lobes on the anterior surface, and they are then easily recognisable during life. In very rare cases the gummatous lesion has extended to neighbouring parts, infiltrating the lower lobe of the right lung through the diaphragm, or invading the anterior abdominal wall. Some degree of calcification is not uncommon, and rarely softening occurs, and, presumably through secondary infection, an abscess may result. The usual end of the gumma is caseation, with complete or incomplete absorption and replace-

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ment by fibrous tissue. The final result varies with the number, size, and position of the gummas. On the one hand, when they have been small and superficial, a few puckered scars with a little thickening of the peritoneum may be the only relics. On vertical section such a scar can be seen to enter the liver substance for a short distance, and perhaps microscopical examination will reveal in it a speck of unabsorbed caseous material. In the opposite extreme the liver is grossly deformed. The whole or a large part of the organ is seamed and traversed in all directions by broad fibrous bands, which on section are seen to separate large irregular masses of liver tissue. According to the stage at which the process has arrived, these bands may or may not still enclose caseous foci visible to the naked eye. In consequence of their contraction the surface of the liver may be scarred and furrowed; or it may come to present rounded eminences separated by deep depressions; or it may become largely lobulated, so that its appearance has been compared to that of the kidneys of young animals. Sometimes the depressions on the surface are so deep and close that the intervening and protruding portions of liver tissue become almost polypoid in form. There is also commonly some degree of general inflammatory thickening of the peritoneal covering of the liver, which may be firmly adherent to the diaphragm and surrounding structures. By the constricting effect of the fibrous bands some local atrophy is produced, but apart from this the bulk of the hepatic tissue is usually unaltered; though occasionally lardaceous change occurs locally round a gumma, and more rarely a general lardaceous transformation is added.

The *symptoms* of hepatic gumma fall into two groups. (*a*) When they are situated on the anterior surface, as is commonly the case, they are readily felt, and even after their absorption the scars and intervening elevations of liver tissue can be appreciated by the hand. Occasionally so large a tumour is felt that the suspicion of carcinoma at once arises. During their active stage discomfort or pain in the right hypochondrium or epigastrium, rarely also in the back, is the prominent symptom, and the liver, which is commonly slightly enlarged, is often tender. The pain, which is doubtless due to local peritonitis, may be very severe. During this stage also there is often some general failure of health, anaemia, and even fever. Sometimes symptoms are slight or absent, and gummas or scars are found unexpectedly after death. (*b*) In the second group ascites is the prominent feature. This is probably due to the mechanical interference exercised by a gumma or its resulting scar-tissue on the intrahepatic branches of the portal vein, but it is possible that a syphilitic perihepatitis may become a general chronic peritonitis and that the ascites is then of peritoneal origin. Jaundice also may result from interference with the main hepatic bile-ducks; but it is far less common than ascites. It may be difficult to distinguish this condition from portal cirrhosis. A history of syphilis and a palpable irregularity of the surface of the liver are important points in the one direction, whilst cirrhosis is indicated by an alcoholic history and by the early

gastro-intestinal symptoms of that disease. Moreover, haematemesis, dilated veins in the abdominal wall, and enlargement of the spleen are more common in cirrhosis. For the diagnosis between syphilitic and malignant disease of the liver, see p. 213.

(2) Some degree of local *perihepatitis* is almost invariable in association with gumma. It is the cause of pain, but it is doubtful if, while strictly confined to the surface of the liver, it gives rise to ascites. A general chronic perihepatitis, however (see p. 164), is met with in conjunction with a diffuse chronic peritonitis affecting all parts of the abdomen, of which condition in fact it forms a part. It is uncertain how far syphilis can be regarded as its cause. Of 22 such cases, collected by Dr. Hale White, syphilis was apparently a factor in 3. Others, however, attribute much greater importance to syphilis in this respect. Though ascites is common in this condition, jaundice is exceedingly rare.

(3) As already pointed out, local *lardaceous* change may be found around a gumma. Sometimes the whole organ becomes lardaceous, with or without gummatous lesions. Enlargement of the spleen and albuminuria are then commonly associated, and, if the resulting anaemia be severe, the case may bear a close resemblance to one of splenic anaemia.

(4) Finally, it is matter for speculation, not admitting of proof, whether there may be a parasyphilitic element in the causation of some cases of multilobular cirrhosis. On this supposition syphilis would have the same remote effect in this condition that it certainly has in arteriosclerosis, tabes, and general paralysis.

(B) INHERITED SYPHILIS.—(1) In infants born with inherited syphilis or speedily developing the signs of it the liver is very commonly affected. The characteristic condition is a diffuse hepatitis ending in a pericellular cirrhosis. The earliest change is a small-celled infiltration which spreads throughout the whole or a large part of the organ; the cells being derived from proliferation of the connective-tissue cells and of the endothelium of the intralobular capillaries and lymphatics. It can be readily understood that, as the process advances and passes into a fibro-plastic stage, the new fibrous tissue is intralobular and pericellular. The whole liver is packed with formative cells and developing or fully formed fibrous tissue, which affect not only the portal canals but permeates the lobules also, separating cell from cell, so that no trace of the normal lobular arrangement may remain. Miliary syphilomas, not unlike tubercles, or even small caseous gummas, may also be present. By appropriate stains the *Treponema pallidum* can be found in large numbers. In an early stage the liver, though uniformly enlarged, may shew no obvious change except under the microscope. In an advanced condition it is obviously indurated and heavy, smooth on the natural and the cut surfaces; though some perihepatitis and adhesions may be present. Its lobular pattern has disappeared, it has a yellowish-grey or sometimes a flint-like colour, and it may be mistaken for a lardaceous liver, though

lardaceous change is rarely present. The hepatic cells may shew atrophy and granular degeneration. Occasionally apparently new-formed bile-ducts may be seen. The spleen is generally enlarged, and the kidneys and pancreas may shew some interstitial fibrosis.

From this condition the child may be stillborn or die soon after birth. Sometimes the enlargement of the liver appears a few weeks after birth in an apparently healthy child. The liver, which is smooth and firm, may be greatly enlarged and may reach the iliac crest, and enlargement of the spleen is generally associated. Jaundice may occur, probably from a catarrhal condition of the small bile-ducts associated with the pericellular hepatitis. Haemorrhages may appear. Ascites is uncommon. The diagnosis may rest mainly on the presence of other signs of congenital syphilis, the lesions of the skin and mucous membranes, and the malnutrition. Recovery is quite possible under prompt treatment, but the prognosis is grave, especially when jaundice has appeared. This pericellular hepatitis must be taken to correspond to the secondary lesions of acquired syphilis.

(2) A delayed inherited syphilis corresponding to the tertiary stage of the acquired disease is not uncommon. It appears as a rule under the age of twenty years, most commonly in the second decade; but exceptional cases are met with up to the age of thirty, and even later. These patients are often ill-developed (*vide* "Infantilism," p. 486). Other evidences of syphilis are usually present, and interstitial keratitis, characteristic teeth, and disease of bone must be looked for. Considerable arteriosclerosis with narrowing of arteries may occur. Clubbing of fingers has been noted. The condition of the liver is much the same as in acquired syphilis; it is enlarged, scarred, and deformed. Gummas, often more or less calcified, scars, fibrosis, pericellular cirrhosis, and lardaceous change are found in varying combination. Lardaceous disease may be general, and may be the cause of death by uraemia. Perihepatitis is common. The spleen is generally enlarged. As in acquired syphilis, ascites is common, but jaundice is rare. When the patient comes under observation the condition is usually far advanced, and treatment may be of little use.

(3) From the inherited as from the acquired disease it is possible that in some instances of multilobular cirrhosis a parasyphilitic element may be present. Such an opinion is supported by the microscopical appearance in some cases, which suggests that the multilobular fibrosis has actually supervened on a pericellular cirrhosis, and the two conditions coexist.

Treatment.—In all cases of hepatic disease in which acquired syphilis or delayed inherited syphilis is a possible cause, treatment with mercury and potassium iodide should be employed with perseverance, and for this no special directions are needed. It must be remembered, however, that a good result can be obtained only when the symptoms are due to a gumma. If the symptoms are due to cicatricial change, it is improbable that specific treatment can have much effect,

and, as in portal cirrhosis, we must fall back eventually on symptomatic treatment. In inherited syphilis immediate treatment is of the utmost importance, either in the form of hydrarg. c. cret. or by inunction; and the child should be kept under observation for three or four years.

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H. P. H.

TUMOURS OF THE LIVER¹

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SECONDARY CANCER is by far the most common form of tumour of the liver. Thus, I find that in the Clinical Reports of the Medical Wards of Guy's Hospital during the years 1888-1906, both inclusive, there were admitted 244 cases diagnosed at the bedside to be cancer of the liver, of which certainly not more than nine or ten were primary; 46 cases of syphilis of the liver; 45 of abscess; 43 of hydatid, and 28 of sarcoma. The frequency with which secondary cancerous growths take place in the liver is shewn by the fact that at Guy's Hospital during the years 1885-1906, both inclusive, out of about 9500 post-mortem examinations 361 examples of secondary deposits in the liver were met with in the dead-house, and of these at least 330 were carcinomatous; that is to say, secondary carcinomatous deposits are found in the livers of 3·47 per cent of all persons who die in Guy's Hospital, a percentage which nearly coincides with that given by Leichtenstern. Of all persons in whom at death malignant disease is found, about 50 per cent have secondary growths in their liver, and no organ is more often the seat of secondary deposits. Out of 76 cases of secondary carcinoma of the liver Dr. Rolleston found the primary seat to be in the following organs the number of times indicated by the figure after each: stomach, 24; colon, 12; oesophagus,

¹ These will be considered in the order of their clinical importance. Syphilis, abscess, hydatid, are described elsewhere.

10 ; pancreas, 8 ; gall-bladder, 5 ; uterus, 4 ; mamma, 3 ; kidneys, 3 ; bile-ducts, 3 ; and biliary papilla, vermiform appendix, urinary bladder, and ovary, one each.

So many of the symptoms of cancer of the liver are due to physical alteration in shape of the organ that it will perhaps be best to describe first the morbid anatomy.

Morbid Anatomy.—If the patient die soon from the effects of the primary growth, the metastases in the liver may be few and small ; but, inasmuch as the primary growth is usually in some organ, the blood of which is returned by the portal vein, the hepatic tissue often becomes affected early ; and in many instances, therefore, there is an enormous growth of cancer in the liver by the time of the patient's death. Cancer causes the liver to be heavier than any other disease of it ; in a case under my care the liver weighed 19 pounds, and even heavier livers have been recorded ; in Christian's case, in which the extraordinary weight of $33\frac{1}{2}$ pounds was reached, the duration of the disease was, as might be expected, exceptionally long, namely 35 months. The secondary growths take the form of whitish nodules scattered about irregularly in the liver substance, suggesting, by their distribution, that we are correct in believing that cancer elements are conveyed in the portal blood to the liver, and multiply wherever they may happen to be arrested. At the patient's death all the nodules are not of the same age, and they are of various sizes, from those which require a microscope for their detection to those which are as large as a fetal head. In a marked case the organ has bosses all over it, especially perhaps on its upper surface. The older of these are umbilicated, and often there is a little local thickening of the peritoneum over them. The nodules, which at first are more or less globular, grow most easily in the direction of least resistance, and this, to some extent, may explain why cancerous nodules are usually absent from the interior of the liver unless some are also visible under its peritoneal coat. The nodules destroy the hepatic tissue, but they increase more rapidly than they destroy ; hence the enormous weight of the liver in an advanced case. Gradually those which are contiguous coalesce ; so that, on section of the liver, large irregular white masses of various shapes, and rounded nodules, occupying, it may be, several cubic inches, are seen let into the hepatic substance, which is dark by contrast. This striking contrast is often much enhanced by the bright yellow tint of the growth, due to staining by the bile, the dark red due to haemorrhage, and the pale yellow due to fatty change.

The cancer as it grows causes atrophy of the hepatic cells ; hence, even when the liver is very heavy, there is much less hepatic tissue than normal ; what is left appears, however, healthy except that the cells in immediate contact with a cancerous nodule are compressed, and sometimes there is an increase of fibrous tissue in the liver. Although the growth cannot be shelled out from the hepatic tissue, the demarcation between cancer substance and liver substance is very sharp. Injection experiments have shewn that blood-vessels from the hepatic artery grow

into the cancerous growth along its septa. The growth resembles that of the primary seat of the disease ; hence its consistency, its tint, and the amount of juice, obtained by scraping it, all vary. After attaining a certain size the nodules begin to undergo autolysis in the centre, the part farthest removed from the blood-supply. The cancer cells may become fatty and break up, and, consequently, the centre of the nodule becomes yellow, soft, and of the consistency of batter ; and if, as sometimes happens, much of the stroma has softened, most of the growth may be washed away with a stream of water, so that a ragged, shreddy mass of stroma is left behind. The fibrous tissue of the cancer, however, usually contracts as time goes on ; and as this contraction is most marked in the centre, where softening has been greatest, the growth when on the surface of the liver becomes umbilicated. The process of softening sometimes lays open the blood-vessels of the stroma, especially in those rapidly-growing tumours which are from the first red and vascular. Thus considerable haemorrhage may take place into the cancer, which becomes a soft, dark-red mass ; and it may even extend into the substance of the liver itself. Sometimes, in these circumstances, the liver may clinically be found to enlarge very rapidly ; and in rare cases haemorrhage has taken place from a nodule on the surface, and blood has poured into the peritoneal cavity. Often the new growth undergoes yellowish, cheesy degeneration ; and sometimes also clear fluid collects in its interior and takes the place of the atrophied cells, which have become absorbed, and thus a cyst is formed. Usually the new growth compresses some bile-ducts in their course through the liver, which, consequently, becomes stained here and there of a deep yellow colour ; this colour often extends into the cancer masses, and the growth of these into the veins, which is very common, leads to considerable ante-mortem clotting in them.

A cancerous mass may envelop and infiltrate the gall-bladder, but often when this appears to have happened the growth has been primarily in the gall-bladder, and has affected the liver secondarily. In the same way, when, as is not uncommon, a malignant mass is seen to implicate both the pylorus and the liver, the stomach should be regarded as the primary seat. Sometimes cancer of the liver grows directly into the diaphragm, which thus becomes adherent ; and I have seen prominent nodules on the surface of the liver leading to the growth of cancerous nodules on the peritoneal lining of the abdominal wall at the spot in contact with the hepatic growth : this has occurred even in the absence of adhesions between the liver and the abdominal wall, but on the other hand, I have known the adhesions so firm that the liver did not move up and down with respiration, and some of the anterior abdominal wall had to be taken away with the liver in order to remove the organ.

The growth in the liver often leads to the formation of a malignant nodule at the umbilicus ; and in such a case I have seen the whole of the round ligament converted into a cancerous cord. If the growth has been long present in the liver, or if the organ which is the seat of the primary cancer returns its blood into them, the glands in the transverse fissure

will be secondarily enlarged, even to the size of a hen's egg. Their pressure on the common bile-duct leads to distension of the gall-bladder, converts the mottled bile-staining of the liver into a deep yellow staining of the whole organ, and the jaundice of the entire body becomes extreme and persistent. If the cystic duct be compressed, so that no bile can reach the gall-bladder, the latter is found contracted and contains a little mucus only. It is rare for the growth to spread to the suprarenal capsules, kidney, duodenum, or colon. As the secondary cancers of the liver repeat in every particular the histological characteristics of the primary growth, it is unnecessary to give a description of their microscopical appearances, which will be found in treatises on pathology.

It is not unusual to find gall-stones in the ducts or gall-bladder, and consequent dilatation and ulceration of the bile passages may occur. Sometimes the gall-stone by its irritation has set up a primary growth of the gall-bladder or the ducts. It is outside our subject to describe the post-mortem appearances of the primary growth in other organs, the secondary deposits elsewhere than in the liver, the bile-stained condition of the body generally, and the post-mortem signs of death from cancer. It is worth while, however, to point out that whereas metastasis usually takes place by the lymphatics and not by the venous system, in the case of hepatic carcinoma the infective cells are conveyed by the portal vein when the primary seat is in the portal area and by the hepatic artery when it is not ; and that probably the reason why secondary growths in the liver are so common, is that the primary growth, being out of reach of surgical interference, goes on to ulceration, and peripheral twigs of the portal vein are thus laid open.

Although a secondary colloid cancer of the liver repeats the appearance of the primary growth, colloid cancer invading the liver by direct extension from the peritoneum has, according to Schueppel, quite a different appearance ; for the invasion takes place by the lymphatics, and thus we see at first numerous subserous rows of colloid material which, later, run through the liver like colloid strings. Ultimately the organ may thus become one mass of colloid material.

Symptoms.—In more than half the cases the deposit of cancerous nodules in the liver produces no symptoms by which they can be recognised during life, and then, as far as we know, they do no harm. If the secondary growths in the liver cause symptoms, those of the primary growth will exist side by side with those of the hepatic affection. The great frequency of cancer of the pelvic organs and breasts of women explains why the proportion of males to females that die with cancer of the liver is as 3 to 4. In about half the cases in which the liver is obviously affected, the seat of the primary growth cannot be discovered during life ; then it is often found after death in the pancreas, and usually in the head of this organ.

In the following account I shall omit all reference to symptoms due to the primary growth, or common to cancer in any part of the body. The ages of 75 per cent of all patients with cancer of the liver are between

forty and seventy years; rather under 20 per cent are under forty, and rather over 5 per cent are over seventy. Hepatic carcinoma is all but unknown under twenty.

The means by which we can recognise secondary cancer in the liver are:—Both by percussion and tactile examination enlargement of the liver can usually be determined. The increase of the liver may be so great that the patient gains a little weight in spite of his general wasting. It may reach far below the umbilicus, the hepatic dulness may be increased upwards in the mid-axillary line as far as the fifth rib, and on the left side it may blend with that due to the spleen, but as the organ naturally grows in the direction of least resistance, and the heavier it is the more it tends to fall, increase upwards of the hepatic dulness is not common. The edge of the enlarged organ can nearly always be felt to move up and down with respiration; and, as Sir William Jenner remarks, it often appears lower during life than in the post-mortem room, for as the last respiratory movement is expiratory, it is drawn up at death as high as possible. It is quite common, when the patient becomes much wasted, for movement of the enlarged liver and outward bulging of the right lower ribs to be easily visible. The edge feels hard, and, from the presence of several carcinomatous nodules, is often irregular: the nodules can be felt also on as much of the upper and anterior surface as comes below the ribs, so that the whole organ feels irregular, knobby, and hard.

In rare cases the nodules can be made out to be umbilicated, and if this be ascertained it is absolutely diagnostic of cancer: occasionally, if they are either growing or degenerating very rapidly, they are soft, and give an obscure sense of fluctuation. Sometimes, too, a rub can be both felt and heard over the liver. This indicates either some local peritonitis, or the presence of a cancerous nodule in the parietal peritoneum against which a cancerous nodule in the liver is rubbing. Before deciding that a liver is not carcinomatous, the patient should always be made to take a deep inspiration, for this may reveal a nodule that would otherwise remain hidden under the ribs. Sometimes the cancer grows so fast that the enlargement of the liver may be watched from week to week; and occasionally the whole organ enlarges even more rapidly, and individual nodules may become more prominent within a day. This is very strong evidence in favour of cancer, and indicates considerable haemorrhage into the liver. In a few instances the nodules slowly get smaller as they undergo degeneration. In rare cases the new growth infiltrates the whole liver, which is then enlarged and hard; but no nodules can be felt. Another important sign is tangible distension of the gall-bladder, which indicates that secondarily enlarged glands are pressing on the common duct. It has already been mentioned that the umbilicus is often affected, and during life it may be hard and enlarged.

The patient usually, but by no means always, complains of pain in the region of the liver, both back and front, due probably to stretching of the capsule or to some local peritonitis; and, especially when this has occurred, the organ is tender, and he suffers from a cutting pain when he

coughs. Pain is often referred to the right shoulder-joint, a point of considerable diagnostic importance, and it may go down the right arm. I have had but little experience to shew whether the localised cutaneous tenderness is of much importance in cancer of the liver. Probably not, for the patients are very ill and weak, and the tender areas due to the primary disease may well overlap those due to implication of the liver. When the liver is very large the patient experiences a sense of fulness and dragging in the right hypochondrium.

About half the patients who during life present symptoms of carcinoma of the liver are jaundiced ; and this nearly always means that enlarged carcinomatous glands in the transverse fissure are pressing on the common bile-duct : but in some cases the pressure is due to the primary growth, especially if it be in the head of the pancreas ; and occasionally enough of the hepatic ducts in the liver may be compressed by nodules of new growth for jaundice to appear, and then the patient, although jaundiced, may have bile in the stools. Or there may be primary cancer of the bile-ducts (p. 249). It is extremely important to bear in mind that by far the most frequent cause of long-standing jaundice is cancer of the liver, which also produces deeper jaundice than any other common disease ; thus patients suffering from cancer present, in the most extreme form, the symptoms due to circulation of bile in the blood and to its absence from the intestines. The jaundice, too, is permanent ; the only exceptions to this rule are those excessively rare cases in which, although the patient has cancer of the liver, the jaundice is due to a gall-stone in the common duct, which is either passed on or slips back. The skin, deeply and slowly stained by bile, gradually becomes more and more green, and ultimately assumes a peculiar earthy dark-green tint, which, especially if the patient be aged and wasted, is almost diagnostic of cancer of the liver. The other effects of bile in the blood are also evident. The urine is very dark and has a yellowish froth, the numerous scratch marks shew the intense pruritus, the bitter taste in the mouth is very unpleasant, the sweat may be bile-stained, and if, as often happens from secondary growths in the lungs, the patient gets bronchitis or pneumonia, the expectoration may be yellow. Sometimes the pulse is slow ; in rare cases the patient may complain of xanthopsia, and occasionally patches of xanthelasma appear. The usual cause of death is bile-poisoning, or cholaemia as it is named. In such cases, although the end may be rapid, usually the patient gradually becomes more and more drowsy, with in rare cases an occasional convulsion ; day by day his coma slowly deepens ; his breathing becomes shallower and shallower ; at last he cannot be roused, and sometimes for days before he passes away a superficial observer might think that death had already taken place. There are few things more characteristic in medicine than to see an aged grey-haired patient extremely wasted, with dry, dark-green skin hanging in loose folds, lying perfectly still, so drowsy that he is more dead than alive. If we turn down the bed-clothes the liver may be seen deforming the shape of the abdomen ; and it will be noticed that

the sheets are stained yellow, either from urine or sweat. The absence of bile from the intestine causes indigestion and constipation, the motions are pale, they smell horribly, and contain much undigested fat.

Authors differ as to the frequency of ascites. For my own part, I think that it is not so common as jaundice, and that it usually comes on late in the case. It may occur with or without jaundice, the two being associated in only about 20 per cent of all cases of cancer of the liver diagnosed as such during life. The fluid is clear, it is often stained yellowish-green by bile, and, if any of the superficial hepatic growths have bled, it may contain blood. Inasmuch as ascites may be absent when there has been considerable pressure on the common bile-duct to which the portal vein lies so near, it seems reasonable to doubt whether it is due to pressure on this vein; especially as I have elsewhere (p. 165) brought forward evidence that in perihepatitis, in which disease ascites is often such a prominent feature, it is probably due to chronic peritonitis. I think carefully made autopsies will shew that in many cases at least of cancer of the liver in which ascites is present there is also chronic peritonitis due to malignant nodules in the peritoneum. The amount of ascitic fluid is very variable, and occasionally paracentesis is required. As the quantity increases the pain often lessens, and the observer may find it necessary to make a sudden deep depression in the abdominal parieties in order to feel the liver—to dip for it, as the phrase is.

Occasionally the growth extends through the diaphragm and sets up right-sided pleuritic effusion. The effused fluid is then usually blood-stained, and in quite exceptional cases an empyema may form. Even without pleural effusion, if the liver be very large, we find physical signs of compression of the lower part of the right lung. The weight of the liver may also hamper the circulation through the vena cava: if so the superficial abdominal veins will shew up as prominent dark-blue cords on the dark-green wasted skin. Thrombosis may take place in either internal saphena vein, and towards the end of the case a little albuminuria may appear. The spleen is very rarely enlarged. As in many other diseases of the liver, the urine may be loaded with lithates and may contain a considerable amount of urobilin; and as in cancer of other organs, we occasionally meet with indicanuria. Sometimes, as in almost any intra-abdominal malignant disease, the glands above the left clavicle are infiltrated with growth. Rapidly growing carcinoma or sarcoma of the liver is often associated with an evening temperature of between 99° and 101° F. As with carcinoma anywhere there may be a considerable diminution of red cells and haemoglobin together with a slight increase of white cells. I have seen a case, in which the evening temperature was usually 103° F., with a leucocytosis of 18,000, chiefly polymorphonuclears. Rigors rarely occur unless gall-stones or other complications are present together with the growth. Some patients suffer from an annoying reflex dry cough. When cancer is discovered in the liver a thorough search must be made for the primary seat.

Prognosis.—If the diagnosis is correct, death is inevitable. Usually

all is over in less than six months. Sometimes patients die very rapidly, even in a few weeks. I once had under my care a patient who only began to complain of weakness six weeks, and gave up work three weeks, before death; yet he became rapidly jaundiced, and his liver weighed nineteen pounds. On the other hand, life may be prolonged for a year (and some authors say even longer) after the symptoms have declared themselves; it is a point of considerable importance that at any period the condition of the patient may remain stationary for weeks together, and under careful dieting and rest in bed even improve for a time. I once saw a clergyman in whom this respite occurred, and the friends, much to the annoyance of the medical attendant, persistently spread the report that the diagnosis must be incorrect. My experience of malignant disease certainly is that if after a thorough examination we have satisfied ourselves that the patient is suffering from it, we ought to hesitate very much before we surrender this diagnosis.

Diagnosis.—If this rest principally on the physical examination of the liver, many fallacies beset us. One is that the liver may appear irregularly enlarged when it is normal, and the apparent enlargement may be due to hardened faeces in the transverse colon, which is tender from the enteritis set up by them. Bright gives some excellent instances in point in his memoir on abdominal tumours. An enema will generally clear up this mistake. I have seen tumours of the stomach and also the thickened puckered omentum that is found in chronic peritonitis, whether simple, tuberculous, or cancerous, considered to be the thickened indurated edge of a liver affected with cancer. A careful consideration of the shape of the tumour, the detection of the edge of the liver above it, and, in the case of an omental tumour, the discovery of resonance between it and the liver, together with a proper estimation of all the symptoms of the case, should usually prevent this error. I have also known a renal enlargement ascribed to the liver; and in all such cases the error has been largely due to forgetfulness that as the stomach, the kidney, and the colon to which the omentum is attached, touch the liver they may well, like the edge of it, make a considerable excursion during deep breathing. Then, again, tumours in the wall of the abdomen occasionally lead to mistakes, or the liver may appear enlarged when, in reality, its size is unaltered. For example, it may have dropped down as a part of a general visceroptosis, or it may be pressed down by lacing, or by an abscess between it and the diaphragm; a pleural or a pericardial effusion has to be very large to depress the liver; or the line of hepatic dulness may be higher in the chest than normal, because the liver is pressed up by ascites or some large intra-abdominal tumour, but this is very rare, for naturally the abdominal wall is expanded and the intestine is compressed before the diaphragm is pressed upwards. Lastly, an enlargement of the liver may be concealed by tympanites or emphysema.

But even when we have evaded all these fallacies, our difficulties are by no means at an end. Often there is no easier diagnosis in medicine than that of cancer of the liver, but in those cases in which the primary

growth cannot be found it may be very difficult ; and if at the same time the liver is not enlarged, it may be almost impossible. Fortunately such a combination is rare, unless the cancerous deposit in the liver is limited to a few small nodules. In the only specimen of contracting carcinoma we have in the Museum at Guy's Hospital there was a primary growth in the breast. At the bedside the question nearly always takes this form : Is this patient, who has no decided evidence of any primary malignant disease and whose liver is enlarged, suffering from malignant disease of it ? The liver may be enlarged not only by malignant disease, but also from passive venous engorgement, as in heart disease, the active congestion of hot countries, malaria, yellow fever, leukaemia, Hodgkin's disease, pernicious anaemia, diabetes, fatty liver, hydatid, tropical abscess, the single large abscess of those who have never been abroad, suppurating hydatid, actinomycosis, tuberculous abscess, obstruction of the common bile-duct, lardaceous disease, hypertrophic cirrhosis, congenital and acquired syphilis ; moreover, in perihepatitis, if the capsule be very thick, it may appear a little enlarged. The majority of these diseases never present any difficulty ; but the big cirrhotic liver, the syphilitic liver, and, more rarely, obstruction of the common bile-duct, or hydatid, often give rise to much hesitation.

The large cirrhotic liver is uniformly large, and the palpable nodules on the surface of it are small. Sir William Jenner says that if any of them appear bigger than a cherry the case cannot be cirrhosis ; they are never umbilicated, and neither they nor the whole liver ever tangibly increase in size in a few days ; and although pain and tenderness may be present, neither of these is as severe as it usually is in cancer. Although jaundice is seen only in about half the cases of growth, and in about the same proportion of the cases of large cirrhotic liver, this symptom is often the very means of establishing a diagnosis ; for in cirrhosis the jaundice is not commonly very deep, and it always remains yellow ; but in cancer it soon becomes intense, and slowly changes to the characteristic deep dirty-green colour already described. A patient with malignant disease often dies soon after the occurrence of either jaundice or ascites, but he may live many months ; on the other hand, the supervention of these symptoms in the large cirrhotic liver usually points to death in less than ten weeks. The obstruction to the flow of bile is never great enough in cirrhosis to cause distension of the gall-bladder or definitely clay-coloured stools, so that either of these symptoms would turn the scale in favour of malignant disease. The spleen is enlarged in rather more than half the cases of enlarged cirrhotic livers, and but rarely in malignant disease. Regard must, of course, be paid to the history and the age of the patient and to the lack of any other evidence of alcoholic poisoning. The aspect of the patient and the dryness of the skin may suggest cancer, but we must remember that wasting may be extremely marked in cirrhosis. The discovery of an enlarged gland above the left clavicle or of the primary seat of the growth is direct evidence in favour of cancer.

The diagnosis between malignant disease and syphilis may be difficult. Acquired syphilis leads to the formation in the liver of deposits of fibroid tissue and gummas. As the former contract and the latter are absorbed, scar-like depressions mark the surface, and between them the unaltered liver substance, which has undergone compensatory hypertrophy, projects, and these nodules of healthy liver and those of unabsorbed gummas cause the liver to be covered with lumps of all sizes, giving the whole organ on physical examination a close resemblance to a cancerous liver; this is the more embarrassing as, from syphilitic lardaceous disease of it, the total enlargement may be quite as great as is usually the case in hepatic cancer. It is conceivable that the glands in the transverse fissure might be much enlarged from gummatous change—and we have a specimen in Guy's Hospital Museum shewing this; if so they might press on the common bile-duct and cause jaundice and distension of the gall-bladder, but gummatous and lardaceous diseases of the lymphatic glands are pathological curiosities: if then the patient be jaundiced, or his gall-bladder distended, it is all but certain that the enlargement of his liver is not syphilitic. It is, too, within the range of possibility that in the same patient syphilis might not only distort the liver, but also cause perihepatitis and chronic peritonitis, and so induce ascites; however, not only is it extremely unlikely that two rare results of syphilis should be present in the same case, but the perihepatitis would smooth over the syphilitic irregularities on the liver. In a case of doubt, therefore, ascites is very strong evidence in favour of cancer. Other points of distinction are that syphilis never causes the rapid enlargement of the whole liver or its nodules that may occur in cancer; on the other hand, in cancer we never get the marked diminution of both that occurs in syphilis, especially in cases under treatment by iodide of potassium. The liver attains a much greater size in cancer than in syphilis. Pain and tenderness are not so extreme in syphilis as in cancer. Rapidity and great severity of the general symptoms are, of course, much in favour of cancer; and I need hardly add that a careful search must be made for other signs of syphilis. In congenital syphilis the liver may exactly resemble that of acquired syphilis, but as it is always met with in young adults or children it is not likely to be confused with malignant disease.

Cases in which, owing to non-malignant obstruction of the duct, bile is retained in the liver, causing it to be enlarged and the patient to be jaundiced, sometimes present very great difficulty. Sometimes gall-stones have set up chronic inflammatory thickening outside the common and cystic ducts. Bright recorded a remarkable instance in which the parts about the entrance of the common duct into the duodenum were thus hardened and matted together. The common, hepatic, and cystic ducts were dilated to the size of a healthy gall-bladder; and the gall-bladder was so dilated that, both during life and after death, it almost reached the crest of the ilium. The ducts in the liver were dilated into a number of vesicles. The pancreatic duct was also much dilated. The patient, a woman aged fifty-six, gave a history

of spasmodic pains five years before admission. She was jaundiced and had great hepatic pain and pale stools for four and a half months before she died drowsy from cholaemia. She was very sick and wasted much, but the jaundice was never of an olive-green colour ; in fact, it was stated to be brilliant a few days before her death. I saw a lady aged about sixty who had suffered from gall-stones years before. Her present illness consisted of some loss of flesh, much hepatic pain and tenderness, enlargement of the liver, jaundice, vomiting, constipation, and white stools. Here the diagnosis lay between growth and inflammatory thickening. A fortnight before death the jaundice disappeared, but a day or two afterwards symptoms of pyaemia set in. At the autopsy there was so much inflammatory thickening on the under surface of the liver that it took some time to discover the gall-bladder ; this was sloughing, and, except for a gall-stone, empty. The common and hepatic ducts were enormously dilated, and in the former lay a gall-stone easily movable ; and no doubt the accidental shifting of it led to the disappearance of the jaundice. The liver was studded with minute abscesses. The main points of distinction between cancer of the liver and non-malignant obstruction of the biliary passages are that in the latter case the patient does not look as though she were suffering from cancer ; the hepatic enlargement is uniform, never so great as it often is in cancer, and the jaundice does not become dark green. If it disappears for a time, this probably means that a gall-stone has shifted its position ; that the jaundice of cancer should disappear is almost unknown. Usually a gall-stone impacted in the common duct does not give rise to dense inflammatory adhesions around it. The patient hardly ever dies solely from its impaction, as it generally occupies that part of the duct which lies in the wall of the duodenum, and from that position it ulcerates its way into the duodenum and the jaundice disappears. When we are in doubt whether a patient has an impacted gall-stone or a malignant growth, exploration, if done, nearly always reveals a growth.

Hydatid of the liver seldom gives rise to difficulty, for usually the tumours are only one or two, and they are smooth, regular, not tender, cause neither pain, jaundice, ascites, nor general emaciation, and may give a thrill. There is no leucocytosis, but there may be eosinophilia. It is extremely rare for a hydatid tumour to press on a bile-duct, and so lead to jaundice, which is, however, occasionally caused by the rupture of a hydatid cyst into the bile-duct. Such a case may be extremely difficult to diagnose, but our chief guides will be the sudden onset of jaundice, the physical examination of the liver, and the absence of wasting and pain. The exogenous form of hydatid may form multiple tumours, and these and the multiple tumours formed by the alveolar variety may, if they happen to cause jaundice, give rise to great uncertainty. But they are so rare that it will be necessary to think of them in those instances only in which the age, the absence of wasting, and the long duration of the illness lead to the conclusion that the case cannot be one of cancer.

Dr. J. W. Russell reminds us that forgetfulness that pyrexia may be associated with new growth has led to unnecessary operations on the liver.

If pyrexia is present with growth the diurnal variation is not usually as extensive as when pus exists; but I have seen a case in which from the feel of the liver there was little doubt that the patient had malignant disease of the organ, but the wide fluctuations of temperature together with considerable leucocytosis led one doctor to suggest abscess. At an exploratory operation growth was found.

Treatment.—This can only be palliative. Morphine may be given to relieve the pain, and sometimes the pruritus is so intractable that it yields to nothing else. This symptom is often most distressing. Perhaps pilo-carpine subcutaneously or warm alkaline baths are the next best remedies. Constipation and vomiting should be treated on ordinary principles; for the latter it is often of great service to wash out the stomach. The ascites may require paracentesis. A few surgeons have excised a cancerous nodule from the liver, but suitable cases must be excessively rare. Cullen has published a summary of 17 cases in which tumours of the liver have been operated upon between the years 1899 and 1905. Nearly all were angiomas; out of 15 in which the age was stated 10 were forty years old or under.

PRIMARY CARCINOMA OF THE LIVER.—There is no doubt that many cases formerly regarded as instances of primary carcinoma of the liver were examples of secondary growths in that organ.

During the thirty-seven years 1870-1906, both inclusive, 24 undoubted cases of primary hepatic carcinoma have been seen in the post-mortem room of Guy's Hospital, and about 18,500 post-mortem examinations have been made. Therefore, 0·13 per cent of all the persons who die in a large hospital succumb to primary carcinoma of the liver. Eggel gives the proportion as rather less. The ratio of undoubted primary to secondary carcinoma of the liver is about 1 to 21. During these thirty-seven years there were a very few cases in which the growth was by some regarded as primary in the liver, although many other organs were affected; but, inasmuch as the primary seat of these cases must to some extent be a matter of conjecture, they have not been used as a basis for this account. Frerichs gives the proportion of primary malignant disease of the liver (without growth elsewhere) to other cases of malignant disease of the liver as 1 to 5; but the post-mortem examinations of all his cases were made prior to 1861, and I think it probable that improved systematic methods of careful search for the primary seat, and the fact that Frerichs does not allude to the possibility of the primary seat being in the gall-bladder or bile-ducts, will explain the difference between a proportion of 1 to 5 and 1 to 21. The importance of the gall-bladder and biliary passages as seats of primary malignant disease is shewn by the figures collected by Dr. N. F. Ticehurst; among 11,031 autopsies at Guy's Hospital, 45 examples of primary cancer of the gall-bladder (in 43 of these gall-stones were present) and 15 examples of primary cancer of the ducts (in 11 of these gall-stones were present).

There are four forms of primary cancer of the liver. In the most

common form the new growth is deposited in nodules, and the whole liver exactly resembles the organ when the seat of secondary deposits. In Eggel's series 64·6 per cent fall into this group, and the proportion is about the same in the cases from Guy's Hospital.

In another form, often called massive, the growth consists of one large tumour in the liver. A very good instance is recorded by Bright in his memoirs on abdominal tumours; "the tumour within the liver was the size of an adult's head and of rounded form." It was in the left lobe of the liver, and many of the recorded cases have begun there. Schueppel states that such a growth may destroy half the liver, that caseous degeneration and haemorrhages in it are common, but that the portal glands are not often enlarged. Among the cases from Guy's there were two in which one cancerous mass was huge, and the rest were quite small; so that these cases perhaps belong more to this group than to the first. Eggel finds 23 per cent are of this massive variety.

In the third group the cancer cells are uniformly diffused through the liver, and there is a great increase of fibrous tissue in all directions. This often contracts, so that, although at first the liver is larger than normal, later it may be smaller. Among Eggel's 163 cases collected from literature, 12·4 per cent belong to this group. In 3 cases from Guy's belonging to this group the livers weighed respectively 180, 62, and 36½ oz. In these cases the organ is very hard, retains its shape, and looks like a coarse cirrhosis, the nodules varying in size from a pea to a cherry. When cut it also resembles cirrhosis, for there are wide, white, vascular bands of connective tissue running through the organ, the gland tissue between them has vanished, and, according to Schueppel, in an extreme case, every hepatic acinus has been replaced by one of cancer. On scraping, some white fluid may be obtained; but Schueppel states that the retrogressive changes hardly ever go farther than fatty degeneration of the cells, and haemorrhage is never seen; but in 2 of the 3 cases recorded by Fagge some of the cancerous masses were cheesy and shelled out, and in 1 case there was haemorrhage into them. The glands in the portal fissure are rarely affected, the cancer hardly ever grows into the bile-ducts, and only rarely into the portal vein; but it has been described as implicating the gall-bladder. It always begins in the liver-cells and does not arise in the bile-ducts. Secondary growths in other parts of the body are almost unknown. We see, therefore, that this form of cancer differs much from the common variety; and this, together with the naked-eye and microscopical resemblance to cirrhosis, accounts for the fact that some observers often regard as cirrhosis a case which others consider to be primary infiltrating carcinoma. It should, however, be remembered that there is often some increase of fibrous tissue in the other two varieties of primary carcinoma of the liver.

In a fourth form primary carcinoma arises in a cirrhotic liver. This happened in one of the cases of primary malignant disease of the liver which occurred at Guy's Hospital. The patient, a man aged forty-

nine, who had drunk hard, was admitted under Dr. Goodhart in 1892 for ascites and right pleural effusion. When the ascitic fluid was drawn off, a lump was felt in the hepatic region; he was never jaundiced, and he died three days after the paracentesis. The liver weighed 118 oz., and there was extreme cirrhosis in the parts unaffected by the growth, which formed a large mass in the right lobe together with smaller masses scattered about in the rest of the liver. It was a spheroidal-celled carcinoma. Our museum contains this liver, and also that of a man aged sixty-eight, under Dr. Pye-Smith in 1891, in whom at death a spheroidal-celled carcinoma was found in a cirrhoued liver. Want of space prevents a description of the histology of primary hepatic carcinoma, but it will be found in the English translation of Nothnagel's *Encyclopedia*.

Age.—Of ten cases of which I have notes the oldest patient was seventy-one years old, and the youngest twenty-three. Five were more than fifty years old. Of 7 cases (which, as sarcoma is so rare, we may assume to have been mostly carcinomas) recorded in the Pathological Society's *Transactions* from 1871 to 1891 in sufficient detail to be available, and not included in the 11 cases from Guy's Hospital, the oldest patient was sixty-nine years, and the youngest thirty-three; 5 were over fifty. We thus see that it is a disease of adult life, and generally of old age—a conclusion which is equally true of secondary cancer of the liver. But it should be added that lately a few cases of primary carcinoma of the liver in children have been recorded. Drs. Acland and Dudgeon have paid especial attention to these.

Sex.—Considerably over half of Eggel's cases were males, and this also holds good of the cases at Guy's Hospital. This is interesting, for we have seen that secondary hepatic cancer is commoner in women than men,

Symptoms.—As might be expected, the patients are often wasted. sometimes they vomit; often there is constipation, but the stools are never mentioned as being pale. If the jaundice be sufficient, a little bile may be detected in the urine, which in two instances contained albumin.

Jaundice.—Eggel states that it occurs in 61 per cent of the cases. Out of the 11 cases of which I have notes, in 5 there was no jaundice, in 2 it did not appear till just before death, in 3 it was slight, and in 1 it was considerable. Among the 7 cases of the Pathological Society it is only mentioned as being present in 4, and in 1 of these it was slight. We may thus conclude that in primary malignant disease of the liver jaundice may be absent all through the illness; if present it is usually slight and comes on late. We rarely meet with the prolonged dark staining so common when the liver is affected secondarily. The explanation may be that, as the disease is rapidly fatal, there is not time for deep jaundice to supervene. It cannot be entirely because the portal glands are rarely enlarged in primary carcinoma of the liver, for in the only case in which the jaundice was deep it is expressly stated that they were normal; probably the rarity of their enlargement is due to the death of the patient before there is time for their infection.

Ascites.—In seven of the eleven cases there was ascites, and in most

of these it was sufficient to be detected during life. Among the seven cases of the Pathological Society ascites is only definitely mentioned as being present during life in two; and in one other a little fluid was found after death. Eggel says that 53 per cent of the cases have ascites. The growth often grows into and causes thrombosis of the branches of the portal vein, and in some cases this may explain the ascites. Eggel frequently met with oedema of the feet and enlargement of the spleen.

Enlargement of Liver.—The liver, which is usually painful and tender, is always enlarged except in a few instances in which the accompanying cirrhosis by contraction leads to a reduction of weight. In one of the Guy's cases it only weighed 36½ oz. It may be of normal weight, but usually is considerably above this. In one case the enormous weight of 493 oz. (14 kg.) was reached, but anything over 200 oz. is very rare. As might be expected, carcinoma of the right lobe is much commoner than that of the left. The usual weight is from 120 to 130 oz.

Temperature.—As with secondary so with primary carcinoma, the temperature is often raised to 101° F. in the evening. Probably as primary carcinoma usually grows more rapidly than secondary, pyrexia and leucocytosis, and perhaps eosinophilia, are more common.

Prognosis.—Among 10 patients, I find that, after the first symptom appeared, two lived four months, three lived three months, one lived two and a half months, two lived two months, and in one the duration could not be determined. That gives, roughly speaking, an average duration of twelve weeks, and speaking generally, it may be said that primary malignant disease of the liver is usually rapidly fatal; thus forming a striking contrast to secondary malignant disease of the organ in which the patient often lingers for a long while. This conclusion is fully borne out by the cases recorded in the Pathological Society's *Transactions*, for in the four in which it is mentioned the duration was two, a half, three, and two months respectively. Dr. Byrom Bramwell has, however, recorded an exceptional case of nine months' duration.

It appears, therefore, that primary cancer of the liver resembles the secondary form in many symptoms, but that the duration from the first symptom probably rarely exceeds six months. Less important points are that it is commoner in men than in women, pyrexia is perhaps higher and more frequent, jaundice is not often deep olive-green, and if present is usually slight, and the motions are rarely pale. The glands in the portal fissure are not often enlarged. The changes in the blood are the same as in cancer generally.

In one case treated at Guy's Hospital disease of the liver was never suspected. A woman aged thirty-nine was admitted for what was regarded as the vomiting of pregnancy; there was no jaundice, and no one even thought of disease of the liver. Premature labour was induced, but the woman sank. The autopsy shewed that the liver was the seat of extensive malignant growth, and that all the other organs of the body were absolutely normal. A case almost parallel to this is recorded by

Tivy, in which, if the abdomen had not been examined and the liver found to be enlarged, it would have been impossible during life to suspect disease of this organ ; yet the man quickly sank and died.

Drs. Powell White and Mair have described a case in which a primary carcinoma of the liver originated in an adrenal "rest." They refer to 2 other cases (Pepere, S. Phillips and Spilsbury).

SARCOMA OF THE LIVER.—This is either primary or secondary. The primary cannot be distinguished, clinically, from carcinoma, and even after death it is often very difficult to decide between them. I have known different opinions given upon the same section. Its extreme rarity is evident from the fact that none of the 11 cases of primary malignant disease which I have quoted as found in the post-mortem room at Guy's Hospital were sarcomatous, and Drs. Byrom Bramwell and Leith, writing in 1897, were only able to collect 27 cases. A primary sarcoma of the liver, which weighed nearly 17 lbs., is recorded in the Pathological Society's *Transactions*. Some of the cases of primary sarcoma occur in children, but the disease may be met with at any age. Drs. Baumann and Forbes record one occurring in an infant eleven months old ; Drs. Carmichael and Wade one occurring at the age of four months. Both papers give references to 5 other cases occurring in infants. Sometimes there is one large tumour in the liver, or there may be many small ones, or the sarcomatous growth may infiltrate the whole liver.

Secondary sarcomas in the liver exactly reproduce the form of the original growth. They are rarely diagnosed, for the patient usually dies before they give rise to symptoms. In eight years we have had 6 cases at Guy's Hospital. The primary seat was in the bones in 5 cases, but the mediastinum and suprarenals are common seats. The secondary growths are usually very numerous in various parts of the body. In most of the cases there is a solitary growth in the liver, and in one this was $2\frac{1}{2}$ inches in diameter. In one only of the Guy's cases were the secondary growths very numerous, and then they were small.

PIGMENT TUMOURS OF THE LIVER.—These tumours, which are either sarcoma or carcinoma, form such striking objects that museums contain many specimens. They only differ from the sarcomas and carcinomas, already described, in that the growth is coloured black or dark brown ; and under the microscope the cells of the tumours are seen to be of a brown colour, and many contain abundant black pigment granules. Melanotic sarcoma is much more common than melanotic carcinoma, and these sarcomas are almost always secondary to a melanotic sarcoma either in the uveal tract or the skin. Many cases are on record : for instance, Bright gives two, in both of which, from the presence of melanotic growths in the skin, a correct diagnosis was made. In both the liver was enormous. The second case illustrated the usual form, for there were innumerable nodular melanotic tumours in the liver. In the first case the melanotic new growth was diffused uniformly throughout the liver. This diffuse

melanosis is very rare, but is mentioned by Schueppel. In Bright's case some non-melanotic secondary tumours were associated with this diffuse melanosis; and sometimes in the same case we find some of the secondary nodules pigmented whilst others are free. Often only one or two melanotic sarcomatous masses are found in the liver; doubtless because the patient died before others could form. In a specimen in Guy's Hospital Museum there is one tumour only. Sometimes, as in Murchison's case, although numerous, they are so small that they produce no symptoms.

A few cases of primary melanotic sarcoma of the liver are on record (Frerichs, Block, Delépine, Wickham Legg, Holsti). Block records his as an endothelioma, but Schueppel thinks there is no doubt that it was sarcomatous. Probably some of the cases recorded as primary melanotic were really secondary sarcoma, the primary seat being overlooked.

Melanotic carcinoma is excessively rare. I have, however, seen one case. The only symptoms observed during life were progressive wasting and uniform hepatic enlargement. The liver weighed $122\frac{1}{2}$ oz. I made the autopsy, and there is no doubt the growth was primary in the liver. The case is described in full (34). In Prof. Delépine's case the tumour grew so rapidly that the patient positively gained weight. Pigmentary malignant disease has no separate clinical symptoms from ordinary malignant disease; so unless a primary melanotic tumour is discovered during life it cannot be foretold that pigment will be found in the hepatic growths, unless, on exposing the urine of such a patient to the air, a brownish or blackish discolouration of it appears (melanuria), when a tolerably sure indication of the kind of growth would be obtained.

NON-MALIGNANT TUMOURS.—*Adenomas* are perfectly well-defined tumours having the same structure as proper hepatic tissue, except that the cells may be a little larger than is usual, often have double nuclei, and there may be an increase of fibrous tissue between them. The rest of the hepatic tissue is healthy. They are almost always solitary, and we have a specimen in our museum in which a globular mass $1\frac{1}{4}$ inch in diameter protruded from the surface of the liver. It consists, histologically, of normal liver tissue, except that there is an excess of fibrous tissue. The patient was twenty-six years old; he died of strangulated hernia. Very rarely the tumours are multiple, and then they are small. Such tumours are common in dogs. Adenomas hardly ever give rise to symptoms during life, but in one case, at St. Thomas's Hospital, an adenoma of the left lobe was so large that it was operated upon under the impression that it was a hydatid tumour. The term adenoma has been applied to two other forms of solitary hepatic tumour: (a) those derived from a multiplication of the epithelial cells lining the bile capillaries; (b) those due to the growth of adrenal "rests." Both are very rare, and are of histological rather than clinical interest. When in cirrhosis of the liver the multiplication of liver-cells, which is probably compensatory, forms nodules more prominent than ordinary hobnails, they are sometimes called multiple adenomas. There is much

difference of opinion as to the boundary between multiple adenomas with cirrhosis and carcinoma with cirrhosis.

Lymphadenoma.—New formations consisting of lymphoid tissue, either generally diffused through the liver or occurring as nodules, are not uncommon ; but they are only met with in Hodgkin's disease or in leukaemia, and then form but a part of a widespread formation of lymphoid tissue.

Cavernous angiomas of the liver are common, but produce no symptoms during life, unless of considerable size. We have already referred to operations on them. Murchison refers to a case of myxoma and to one of cystosarcoma, but these are too rare to be of any clinical interest.

Cysts of the liver, not hydatid, are very exceptional. Moschcowitz, writing in 1906, could only find 83 cases in medical literature. There are two varieties. First, those not associated with cysts elsewhere. These are of all sizes, and in very rare instances have contained many pints. The liver may contain any number from one or two to dozens, and if they are numerous the organ on section looks like a honeycomb, and may have on its surface the projections due to the numerous cysts. In an extreme case the liver may weigh several times its normal weight. One liver weighed 35 lbs. Probably they are due to obstruction of a bile-duct, and after a time the colouring matter is absorbed and only clear fluid remains. Sometimes haemorrhage takes place into them. They are surrounded by a firm fibrous capsule, and the lining membrane is smooth. The walls between contiguous cysts may break down and thus give a reticulated appearance. A special variety of these cysts is the solitary hepatic cyst. This is very rare, may attain a great size, occurs at the free border of the liver, and has a thin strand of hepatic tissue over it. Mr. Bland-Sutton suggests, and probably correctly, that these cysts arise from dilatation of the bile-ducts which subsequently fuse to form a single cyst. They are only found in women, and are perhaps associated with tight-lacing. He records the case of a woman from whom such a cyst containing two pints of fluid was removed. It is clear that the difficulties of diagnosis may be very great. For further information about these cysts the reader should consult a paper by Mr. Doran. The second variety of hepatic cysts, usually spoken of as "cystic disease of the liver," is almost always associated with cystic disease of the kidney, and in 19 per cent of all cases of cystic kidney the liver is also cystic. They are always congenital, even when found in adult life. It is rarely that they are suspected during life, but when found in infants they are often associated with various deformities. They are commoner in females than in males. Usually they are excessively numerous, easily visible to the naked eye, form rounded swellings on the surface of the liver, and lead to a great increase in its size and weight, but in quite exceptional cases they are only found on microscopical examination. They contain clear fluid. The disease of the liver usually gives rise to no symptoms unless its size is great. The urine is pale, of

low specific gravity, and nearly always contains albumin. The mode of origin is very obscure, and is discussed by Drs. Rolleston, Still, Blackburn, and by Moschcowitz, who states that they are always associated with congenitally aberrant bile-ducts. Dr. Savage and I examined two general paralytics in whom cysts were found in the liver, kidneys, lungs, heart, and brain. In some of the recorded cases of cysts in many organs the cysts were due to post-mortem changes, but it is very doubtful whether cysts are ever so formed in the brain. In the liver such cysts are usually due to the *Bacillus aerogenes capsulatus*, rarely to *Bacillus coli* or other organisms. The foaming liver is of a light colour. It is soft, and when handled gives rise to an emphysema-like crackling. Projecting on the surface, and in the substance of the liver, are innumerable small gas-containing cysts rarely larger than a pea. The micro-organisms lie in great numbers round the cysts. They gain a foothold at death, or, some have thought, shortly before. This condition of foaming liver is naturally best seen in hot weather when some time has elapsed between death and the autopsy. Minute fibromas are occasionally found in the liver in the post-mortem room, but they do not cause any symptoms.

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DISEASES OF THE GALL-BLADDER AND BILE-DUCTS

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UNTIL about 1887 diseases of the gall-bladder and bile-ducks could be adequately considered with diseases of the liver; but the general advance of medicine and its closer alliance with surgery have given these affections a place of their own. I propose to consider the subject under the heads of—(i.) Inflammatory affections; and (ii.) Tumours of the gall-bladder and bile-ducks.

INFLAMMATORY AFFECTIONS.—These may be conveniently considered clinically under the following headings:—(1) Catarrhal inflammation: (a) Acute catarrhal cholangitis; (b) Chronic catarrhal cholangitis; (c) Chronic catarrhal cholecystitis. (2) Obliterative cholecystitis and cholangitis. (3) Croupous or membranous inflammation of the gall-bladder and bile-ducks. (4) Suppurative inflammations: (a) Simple suppurative cholecystitis or suppurative catarrh, or simple empyema of the gall-bladder; (b) Suppurative and infective cholangitis. (5) Ulceration of the gall-bladder and bile-ducks. (6) Perforation of the gall-bladder and bile-ducks. (7) Fistula of the gall-bladder and bile-ducks. (8) Stricture of the gall-bladder and bile-ducks. (9) Acute parenchymatous or phlegmonous cholecystitis and gangrene of the gall-bladder.

1. Catarrh of the Gall-bladder and Bile-ducks.—The larger bile-ducks and the gall-bladder, being lined with mucous membrane having a cylindrical epithelium and ordinary racemose glands, like other mucous passages, are subject to catarrh which may be acute or chronic.

(a) *Acute catarrh* is supposed to give rise to that evanescent form of icterus, known as catarrhal jaundice, which more frequently occurs in young persons, usually comes on as a sequence of dyspepsia or as a result of exposure to cold, and is ordinarily unaccompanied by pain or serious illness; medical help is sought on account of the marked objective symptom of jaundice. When it is borne in mind that the bile-ducks have a small calibre, that the mucous lining is capable of swelling, and that the secretion of bile takes place under very low pressure, it is easy to suppose that catarrh in this situation may lead to jaundice, though absolute proof of this causation is wanting, as simple catarrhal jaundice furnishes no necropsies. Fagge, indeed, doubted that catarrh of the bile-ducks gives rise to swelling of the mucous membrane. He says:

"A more probable suggestion is that catarrh of the duodenum obstructs the oblique and narrow passage of the duct through the walls of the gut." If so, we may ask why jaundice does not more commonly follow what is probably a frequent disorder. Moreover, we should expect a chronic catarrh to produce permanent jaundice.

I believe that the usual cause of so-called acute catarrhal jaundice is extension of inflammation from the duodenum to the pancreatic duct with a consecutive catarrhal pancreatitis, and as the common bile-duct traverses the pancreas in 62 per cent of cases, it necessarily follows that a swelling of the head of the pancreas may, by pressure on the bile-duct, lead to obstruction of the bile-flow, and so to jaundice. This I have proved in a number of operations undertaken for so-called chronic catarrhal jaundice which had failed to yield to general treatment, and which was cured by cholecystotomy or by cholecystenterostomy. I had the privilege of first pointing out this explanation of acute and chronic catarrhal jaundice in 1900 (6), though I first observed and recognised the condition in 1891. Besides gastro-intestinal catarrh and catarrhal or interstitial pancreatitis, there must also be mentioned, as causes of catarrhal jaundice direct or indirect, exposure to cold, extension to the bile-ducts of inflammation from the parenchyma of the liver, carcinoma of the liver, gall-stones, hydatids, pneumonia, and other acute inflammations and infectious fevers. Murchison gives gout and syphilis as causes, and under this head Fagge includes jaundice due to fright and that occurring in epidemics. Although it is well known that in cancer of the liver jaundice is a very variable sign, it is not always recognised that the icterus is at times dependent on an associated catarrh which may be relieved by treatment, though the original disease persists and progresses. The same remarks apply with almost equal force to alveolar hydatids.

The symptoms of acute catarrh of the bile-ducts (catarrhal jaundice) may be so slight that the patient may know nothing of his condition until he is told that he is yellow; but ordinarily symptoms of gastro-intestinal disturbances—such as coated tongue, bad taste, eructations, want of appetite, nausea and sickness—precede the jaundice. According to the duration of the jaundice, so will be the interference with health and with the general nutrition of the patient. Enlargement of the liver or of the gall-bladder is not seen in slight cases; but, if the affection be prolonged, the liver may be swollen and the gall-bladder somewhat enlarged. In ordinary circumstances the symptoms pass off in two to six weeks, and the patient may feel quite well some time before the jaundice has quite disappeared. In other cases, especially if carelessly treated, the disease may drag on for weeks or months, the liver enlarging and considerable emaciation taking place, so that the question of serious organic disease has to be considered. When the symptoms depend on simple catarrh, recovery usually takes place under proper management; but if the acute catarrh complicate some other disease, the symptoms will depend on the cause, and may be both serious and persistent.

Though other symptoms may be almost absent, catarrhal jaundice always demands the most careful consideration, lest the case turn out to be one of acute atrophy of the liver; which, however, is fortunately an extremely rare disease. The absence of serious symptoms (especially of delirium and rapid pulse) and the usually speedy recovery under treatment are, as a rule, sufficient to enable a diagnosis to be made; but, as Dr. Donkin pointed out in reporting a case of malignant jaundice in a child two years of age, "a practical lesson to be learned from such cases is to be very guarded in the prognosis of all so-called and apparent cases of 'simple' or 'congestive' or 'catarrhal' jaundice in children, when the jaundice does not abate within a week, and still more when it increases." The absence of pain and of the preceding characteristic gall-stone attacks will ordinarily distinguish simple catarrh from that accompanying cholelithiasis. Moreover, the jaundice in cholelithiasis usually passes off rapidly, or, if persistent, is generally intensified after pain, and is often associated with ague-like seizures. In cancer, catarrh of the bile-ducts is probably the chief cause of the jaundice; but loss of flesh, ascites, and nodules or tumour of the liver usually afford sufficient data for diagnosis.

In cirrhosis, the slighter degree of jaundice, the usually more advanced age, the frequent history of drunken habits, and the ascites, together with the generally more serious symptoms and the physical examination of the liver, afford in nearly all cases sufficient help to prevent mistakes. As a rule it may be said that jaundice in a young person coming on without pain, or any apparent cause except disordered digestion, is most probably catarrhal.

Treatment.—A light simple diet and mild saline aperients are indicated. If other medicine be thought necessary, a simple rhubarb and soda mixture will answer well. Half a pint, or a pint, of the natural Carlsbad water, taken warm the first thing in the morning, is often of service as an aperient; if this be insufficient, a teaspoonful of Carlsbad salts can be added, or these salts may be taken in plain hot water. As a rule the patient need not be put to bed, but he should be warmly clothed and avoid chills. If the cause be chill, a warm bath with hot applications over the liver and a diaphoretic medicine will be advisable. Salicylate of sodium is said to be of service. As in jaundice the bile is principally excreted by the kidneys, it is important to maintain their action by diluent drinks and by other diuretics if required. When the jaundice is long continued, the administration of ox-gall and of liquor pancreaticus will assist the assimilation of fats; and creasote may prove of service as an intestinal antiseptic. Rectal injections of hot water, from one to two pints daily, at a temperature of from 60° to 90° F., to be retained as long as possible, are said to prove beneficial by causing a contraction of the gall-bladder which may overcome obstruction due to accumulation of mucus in the common duct.

(b) *Chronic catarrh of the bile-ducts* may be simply a sequel of the acute form; it may then give rise to a more or less persistent jaundice

leading to a suspicion of more serious organic disease. Although dyspeptic symptoms are present, due to the associated gastro-intestinal catarrh and jaundice, and some loss of weight, yet the retention of bodily strength, and the absence of such serious sequels as ascites, haemorrhages, and so forth, generally suggest a good prognosis; moreover, the symptoms usually yield to proper treatment.

Catarrh of the bile-ducts probably always accompanies jaundice from whatever cause ; and, as Moxon pointed out, when an obstruction in the common duct is complete, a colourless mucus is always found in the bile-channels. A search through the pathological records of Guy's Hospital for twenty years failed to discover any exception to this rule. When the obstruction is partial the mucus may be charged with bile, as the backward pressure is not sufficient to stop the secretion and the pouring out of bile into the ducts.

As a concomitant of cancer of the liver and of the bile-ducts, chronic catarrh is common, and is frequently the cause of the accompanying icterus. Thus the relief to the jaundice afforded by treatment in a necessarily fatal disease is accounted for ; whereas when the jaundice is dependent on pressure of the growths on the ducts, it will be slightly or not at all influenced by remedies. The same remarks apply to the effects of hydatids, of abscess, and of other organic diseases of the liver. Gall-stones are probably always accompanied by catarrh and by the formation of thick,ropy mucus which, as it passes, sets up attacks of pain ; and it seems not unlikely that some minor seizures of pain, followed by little or no jaundice, are of this nature—in which case, of course, no gall-stones will be found in the evacuations.

As the chief cause of catarrhal inflammation of the bile-ducts is an extension of catarrh from the duodenum, and as the common bile-duct and Wirsung's duct both terminate in the ampulla of Vater, it necessarily follows that the pancreatic duct participates in the inflammatory process. The effect of an inflammation extending up the pancreatic duct is to cause a swelling of the pancreas itself, which if chronic assumes the form of interstitial pancreatitis. As the termination of the common bile-duct is embraced by the pancreas in 62 per cent of cases, and runs in a groove in the gland in the remainder, it necessarily follows that when the pancreas becomes swollen by inflammation the common bile-duct becomes compressed, thus keeping up the jaundice and giving rise to so-called chronic catarrhal jaundice. When the obstruction is great the jaundice is extreme, and the enlargement of the liver associated with great loss of weight and strength naturally gives rise to a suspicion of cancer of the head of the pancreas, or to other serious disease (see also 5, 6, 7, 8).

Chronic catarrhal jaundice needs practically the same treatment as the acute form : careful dieting, regular exercise, a saline aperient in the morning, and an alkaline medicine being the chief means required. In case the disease prove obstinate, treatment at Carlsbad or Harrogate will probably be of service. Should the catarrh depend on organic disease,

the treatment may require modification to meet the special features of the case.

(c) *Chronic catarrh of the gall-bladder* without jaundice forms a distinct and definite disease ; and I have seen several cases in which careful observers had diagnosed cholelithiasis and had recommended operation, but in which neither the gall-bladder nor ducts contained anything firmer than thickropy mucus, which seemed to be the cause of the painful contractions of the gall-bladder simulating gall-stone colic. In one case of this kind, in a lady of fifty-six on whom I operated, the gall-bladder contained bile mixed with thick mucus, which formed plugs something like small grains of boiled sago. There were no other signs of disease, but the gall-bladder was very large and pouched and its mucous membrane thickened. The gall-bladder was drained for a fortnight, and the wound was then allowed to close. The patient continues well, and is free from her formerly frequent attacks. In several similar cases I have found equally good results to follow simple cholecystotomy.

Although in these cases the gall-bladder is usually distended it rarely forms a distinct tumour, and there is an absence of pain on pressure over it. Unless gall-stones have been present at some time there are usually no adhesions of the gall-bladder or ducts to the neighbouring viscera. This proves that the inflammation has not penetrated to the peritoneal coat, as usually it does when dependent on gall-stones.

This catarrh may be the sequence of gall-stone irritation ; but in other cases it may be due to the dependent position of the fundus of the gall-bladder, or to chronic constipation and accumulation of faeces in the hepatic flexure of the colon interfering with the regular emptying of the gall-bladder. It is probably always actually due to a mild form of infection of the mucous membrane.

The diagnosis of this affection from cholelithiasis may usually be made by observing that the attacks are less severe and less prolonged than in gall-stone colic ; that no gall-stones are found in the evacuations after an attack ; that jaundice seldom supervenes, or if it does is only very slight ; that there is no tenderness on pressure between the ninth costal cartilage and the umbilicus, and that the affection, as a rule, will yield completely to treatment. Should medical treatment fail to give relief, it may be difficult to distinguish chronic catarrh of the gall-bladder from cholelithiasis ; but if, under the belief that the case is one of gall-stones, the gall-bladder be exposed and no concretions found, drainage of the gall-bladder will probably effect a cure.

In chronic catarrh of the gall-bladder, regular exercise, massage over the hepatic region, the avoidance of anything tight round the waist (which will increase the dependence of the fundus of the gall-bladder), careful regulation of the diet, and the judicious employment of saline aperients, should in all cases be recommended. A tumblerful of the natural Carlsbad water, with a little hot water, taken before breakfast each morning, and every other morning, in addition, a dose of Carlsbad salts, or of sulphate of magnesium, are undoubtedly useful ; as is also

an alkaline tonic containing soda and nux vomica before lunch and dinner.

The spasmody attacks may require the administration of a sedative: if slight, 5 to 10 grains of aspirin, repeated in an hour, will often relieve the pain; or 20 drops of spirit of ether in half an ounce of chloroform water, the dose to be repeated every fifteen minutes until relief is obtained. The application of hot fomentations, and the administration internally of a pint of hot water, will at times afford efficient relief; but in some cases nothing short of a subcutaneous injection of morphine will suffice. If, after a few weeks of general treatment, the symptoms are not relieved, the disorder will probably be attributed to gall-stones, and operative treatment will be considered. If the gall-bladder and ducts be found free from gall-stones, cholecystotomy and drainage should nevertheless be performed; and it will be found useful after the third day to syringe sterilised hot water gently through the drainage-tube daily so as to wash out the ducts; after a fortnight the tube may be left out and the wound allowed to close. General treatment directed to the cause should be continued for some time afterwards.

2. Obliterative Cholecystitis and Cholangitis.—It is now well recognised that repeated attacks of appendicitis may ultimately lead to obliteration of the vermiform appendix, which may be discovered as a simple cord without any lumen, in firm adhesions. The same result may be brought about in the gall-bladder and bile-ducts by repeated attacks of inflammation, so that it is not very uncommon to find the gall-bladder and cystic duct represented only by a fibrous cord, surrounded by adherent viscera, and unless carefully sought for, it may be thought that they have been congenitally absent. Between this form, which may be conveniently termed obliterative cholecystitis, and the ordinary contracted gall-bladder so frequently seen in operations for gall-stones, every degree of deformity may exist. The gall-bladder may be only partly obliterated, and the small amount of mucous membrane left may continue to secrete a little mucus, and keep up a constant state of irritation resembling true gall-stone seizures; or the cystic duct may be obliterated, and the gall-bladder may form a cyst containing mucus quite separated from the bile-channels proper. In nearly all these cases the recurring pains call for operation, and unless the apparently insignificant and almost obliterated remains of the gall-bladder be taken away, the attacks of pain, often associated with fever, will continue, and lead to serious deterioration of health. In obliterative cholangitis of the common or hepatic ducts permanent jaundice occurs with retention of bile in the liver, leading to cirrhosis and ascites that may continue for years; in one case on which I operated the common and hepatic ducts formed a hard cord imprisoning at intervals here and there small gall-stones; the veins of the abdomen were enormously enlarged, the portal vein being $1\frac{1}{2}$ inch in diameter. The gall-bladder was almost obliterated.

Treatment.—The direct drainage of an hepatic duct in the substance of the liver, or the establishment of a channel between it and the

duodenum, have both been suggested and even attempted in similar cases, but the operations must as a rule be impracticable, always extremely dangerous, and offer but a slender chance of relief. (For congenital obliteration of the bile-ducts, see p. 103.)

3. Membranous Inflammation of the Gall-bladder and Bile-ducts.

—It had been noticed, as far back as 1820, by Dr. Richard Powell that membranous or croupous enteritis was frequently associated with attacks simulating gall-stone seizures; and Mr. Jonathan Hutchinson, in commenting on this paper, suggests that in some of these cases a *bona-fide* attack of gall-stone colic may have been the cause of the membranous enteritis. From a number of cases that I have seen and observed, some of them having been submitted to operation without finding gall-stones, but in which there was abundant evidence of inflammation of the gall-bladder and bile-ducts, I have formed the opinion that the cause of the painful attacks, followed by slight jaundice in these cases of membranous enteritis, is the formation of membranes in the bile-passages, which, partly obstructing the bile-flow, sets up spasm of the gall-bladder, just as a gall-stone or even a lump of tenacious mucus will do. Owing to the disintegrating effect of the bile and of the intestinal secretion, it seldom happens that a true cast of the gall-bladder or bile-ducts is discovered, as occurred in the following case related by Dr. Clennell Fenwick concerning a patient he had seen with Dr. Brittin. “A. B., aged twenty-nine, has had nine attacks of biliary colic in the last fourteen months, accompanied by more or less severe jaundice. During the first two attacks he passed on each occasion a fairly large faceted gall-stone. The faeces had not been examined during the later illnesses; but from the severe pain and the symptoms, exactly resembling his earlier attacks, he feels sure that he has passed a stone on each occasion. Fourteen days ago he had a severe colic, necessitating the use of morphine, and next day passed a large piece of flesh, which was examined by his doctor, who describes it as an oblong sac with moderately thick walls, stained green, about two inches long and one inch broad, resembling the gall-bladder in shape. Ten days later he was again seized with severe pain, similar to that experienced in all the former illnesses, and after some hours of agony he was relieved, and next day passed another cast, which I examined. It is two inches long, and one and a half inches in breadth, its walls are one-tenth inch thick, it is a closed sac with a distinct neck, and is stained bright green in parts, especially towards the neck. When laid out it appears to resemble a gall-bladder. The accompanying faeces were clay-coloured, and had been so for a long period of time. There was no microscopic appearance of hydatid structure, and I do not think that it was an intestinal cast. We came to the conclusion that both these casts were derived from the gall-bladder, as the patient had suffered from typical biliary colic many times before, and described the pain experienced before the passage of the casts as exactly similar to that he had felt before he passed the gall-stones. It does not seem improbable that the presence of these stones had set up a chronic inflammation in the bladder

which had resulted in the formation of a false membrane, which had itself been expelled after the last stone had been passed."

Diagnosis.—As the symptoms so exactly resemble gall-stone attacks, the disease can only be differentiated by an examination of the evacuations, when the discovery of membranous intestinal casts will raise the suspicion of membranous cholecystitis or choledochitis. Should a cast of the gall-bladder be discovered, the diagnosis will be rendered certain, but in the absence of such positive evidence the possibility of gall-stones being also present will be entertained.

Treatment.—If under treatment by saline aperients, such as Carlsbad salts given the first thing in the morning, and careful dieting, the symptoms do not abate, the question of drainage of the gall-bladder by cholecystotomy will be well worth considering, and at the time of operation adhesions of the gall-bladder to the neighbouring viscera, which will probably be found, should be broken down. I have also recorded two cases treated successfully by cholecystotomy (12).

4. *Suppurative Inflammation of the Bile-Passages.*—At first sight suppurative inflammation of the gall-bladder and bile-ducts would seem to be capable of description in small compass and under one heading; but the subject is by no means so simple as it would appear.

For instance, *simple empyema or suppurative catarrh of the gall-bladder*, which is closely allied to suppurative cholangitis, differs altogether from phlegmonous cholecystitis; this latter, however, is also associated with pus in the gall-bladder, and may thus quite properly be called an empyema. Phlegmonous cholecystitis, however, if not operated on expeditiously, is one of the most fatal of diseases, as not only is there a tendency to gangrene, but also to a rapidly spreading and lethal peritonitis. The different clinical characters of suppurative inflammation can probably be accounted for by the presence or absence of certain organisms; and although the bacteriology of this lesion is not yet complete, sufficient good work has been done to make a review of it well worthy of consideration. It has been supposed that the bile is an antiseptic fluid which tends to prevent decomposition in the alimentary canal; but in a series of observations published some years ago on a case of biliary fistula, I found that the absence of bile from the intestine of a woman during a period of fifteen months did not lead to any irregular fermentative process; the alleged antiseptic effect of bile on the faeces is, therefore, probably imaginary. Normal bile is always sterile: this was proved by Netter in 1884, who experimented on dogs, and the fact has been confirmed by Gilbert and Girode, and, later, by Naunyn, who found it sterile in two cases within a few hours of death. On several occasions I have been able to prove the sterility of normal bile in the human subject when it seemed advisable to ascertain the condition of the secretion during an exploratory operation. In a case of mucous fistula, due to stricture of the cystic duct, the constantly clean appearance of the edges of the fistula suggested to me that the fluid secreted by the gall-bladder might possess antiseptic properties; moreover, when collecting the fluid

for experimental purposes, I found I could leave the flasks exposed to the air for several days without any apparent change, an observation which strengthened the presumption. Professor Birch, to whom I supplied some of this fluid, performed numerous cultivation experiments, and came to the conclusion that its antiseptic properties were but slight, the want of change being probably due to poverty of the fluid in nutrient materials. When, however, the flow of bile from the cystic duct is arrested, micro-organisms often enter the gall-bladder ; and Charcot and Gombault, after ligaturing the common duct in dogs, demonstrated the presence of organisms within the gall-bladder. This observation was confirmed by Netter, who found that twenty-four hours after aseptic ligature of the common duct in dogs, organisms—a staphylococcus and *B. coli communis*—could be cultivated from the bile.

In simple catarrhal empyema of the gall-bladder, organisms are not necessarily present ; for instance, I operated on a case in which a tumour of the gall-bladder had been present for a year, and removed sixteen gall-stones and two ounces of thick mucopus, but no organisms could be found. In this case the walls of the gall-bladder were not thickened, and the serous coat was free from inflammation. Moreover, there were no adhesions except over the cystic duct, where the largest gall-stone had been impacted. On the other hand I have frequently found streptococci, *B. coli*, and staphylococci in simple empyema of the gall-bladder, and even in the bile from an infected gall-bladder before pus had formed.

In acute or phlegmonous cholecystitis the walls of the gall-bladder are swollen and oedematous, and they may be infiltrated with pus. In three out of five of such cases Naunyn found the *B. coli communis* in the pus ; and in a large number of cases in which I have performed cholecystectomy for phlegmonous cholecystitis this organism has always been discovered. Though there be no perforation, the spread of infection through the walls of the gall-bladder may occur in these cases, giving rise to virulent peritonitis. Gilbert and Girode found typhoid bacilli in the pus from a case of empyema of the gall-bladder which came on as a sequence of enteric fever, and many other observers have shewn the gall-bladder and bile-ducts to be a favourite nidus for typhoid organisms both during the acute stages of enteric fever and for some weeks after convalescence has been established. Gilbert and Dominici also assert that they produced suppuration in the gall-bladder and liver of rabbits by injecting a culture of typhoid bacilli into the common duct. These biological facts are borne out by the clinical observations of Murchison and Dr. Hale White, who found evidence of inflammation and ulceration of the biliary passages in well-marked and fatal cases of enteric fever.

From the foregoing observations it would seem that though the bile-channels and their contents, under ordinary conditions, are free from organisms, their proximity to the intestinal canal, where bacteria abound, renders them liable to invasion ; infection does not usually occur,

however, when the organs are healthy, but only under some abnormal condition such as gall-stone obstruction or typhoid ulceration.

Infective cholangitis, or infective catarrh of the bile-ducts, is usually due to gall-stones in the common duct, which favour the entrance of organisms from the intestine through the duodenal orifice. Courvoisier, Osler, and Fenger have each described the ball-valve action of gall-stones in a dilated common bile-duct or in the ampulla of Vater; thus accounting for the intermittent character of the jaundice and the irregular course of the disease. Charcot was one of the first to describe the disease under the name of *intermittent hepatic fever*. I have operated on a considerable number of cases of infective cholangitis dependent on gall-stones in the common duct, but although on many occasions the gall-stones were floating and acting like a ball-valve, in others they were multiple and more or less impacted.

The usual history is one of spasms for several years without jaundice; then comes a more severe seizure followed by temporary icterus. If the gall-stone pass, there is an end of the trouble; if not, the next attack of pain is probably followed at once by a shiver and by all the symptoms of an "ague fit," the temperature frequently reaching 104° or 105° F. After it has passed off, the skin is more deeply tinged and the jaundice may persist, though inconstant in degree; it rarely, however, disappears completely between the attacks; there is usually a slight icteric tinge of the conjunctivae, even though the interval between the attacks may be one of weeks or months. The rigors may be repeated daily or at irregular intervals. The gall-bladder may be felt as an enlargement below the right costal margin, but this is not usual, as if gall-stones be present it is more common to find the gall-bladder contracted. The liver at first is not enlarged, but later it may descend considerably. Tenderness over the gall-bladder or in the epigastric region can generally be elicited. There is usually well-marked loss of flesh and strength; and, if unrelieved by nature or art, the disease may run on into suppurative cholangitis and its complications.

Infective cholangitis may persist off and on for years, and may end in recovery if the obstruction be removed; on the other hand, it may assume an acute form and lead to death from pain, biliary toxæmia, and exhaustion. The complications which may follow are diffuse hepatitis, abscess of the liver, cholecystitis, and empyema of the gall-bladder, perforation of the ducts, acute, subacute, or chronic pancreatitis, endocarditis, pleurisy, pneumonia, and other septic diseases.

Diagnosis.—Ague, being now a rare disease in England, is not so readily assumed as it is in countries where malaria is endemic, though the regularity of the chills and the slight jaundice and enlargement of the spleen in some cases may suggest it; yet the pain and tenderness, the history of cholelithiasis, the absence of the specific organism in the blood, and the failure of relief by large doses of quinine, soon settle any doubts. I have operated on several cases of common-duct cholelithiasis that had for many months been mistaken for ague and treated as such

without relief, which completely cleared up after the removal of concretions from the common duct.

As infective diseases in the bile-passages are prone to end in suppuration, abscess of the liver and suppurative cholangitis may supervene; but the more prolonged course of infective cholangitis, the comparative good health between the attacks, the irregularity in the course of the disease, and the absence of rapid and progressive deterioration of health will usually enable a diagnosis to be made. When suppuration exists we usually find increased tenderness over the liver area, continued or irregular intermittent fever, and intense and persistent jaundice.

Treatment.—If possible the cause should be removed by choledochotomy, when at the same time the ducts can be drained; fortunately this may be accomplished with every prospect of success if, as is commonly the case, the primary disease be gall-stones. In my latest series of common duct cases, out of 150 choledochotomies that I personally performed the mortality was under 4 per cent. There can be no doubt in the minds of those who have observed many of these cases that it is better to anticipate the complications; and that as soon as medical treatment has been fairly tried and failed, the removal of gall-stones by surgical means should be resorted to, when as shewn by a series of some hundreds of cases occurring in my practice, the rate of mortality is less than 1 per cent.

Suppurative cholangitis is a subject of considerable interest both to the physician and surgeon. Its gravity lies not only in its causation, but in the combined effects of biliary obstruction with pyogenetic infection, and their local and constitutional effects also.

Etiology.—The most frequent cause is gall-stones, and of this series the museums furnish many examples. One in Guy's Museum shews the ducts throughout the liver inflamed, dilated, and associated with several small abscess cavities; the cause being a gall-stone floating in the common duct. The parts were taken from a woman, aged thirty, who had had enteric fever five months before death; the death was due to pyrexia accompanied by rigors. But, besides gall-stones, hydatid disease, cancer of the bile-ducts, enteric fever, and influenza may cause suppurative cholangitis; and I suspect that the disease not infrequently accompanies other acute infectious ailments. There are good examples of cholangitis due to hydatid disease in St. Bartholomew's, Guy's, St. George's, and the Middlesex Museums; so that it is evidently no infrequent cause. In some of these instances a hydatid cyst has burst into a bile-duct, and in several of these a piece of rolled-up hydatid membrane projects through the papilla into the duodenum. In all these cases the ducts throughout the liver are dilated and filled with pus. Some years ago I operated on a case of suppurative cholangitis dependent on malignant disease in the common duct. The patient was decidedly relieved for a time by the drainage established by cholecystotomy; he ultimately died, however, from the original disease, and at the autopsy the whole of the ducts throughout the liver were filled with mucopus. A very good example of

suppurative cholangitis arising as the result of cancer of the ampulla of Vater may be seen in St. Thomas's Museum. In enteric fever the disease arises irrespective of any organic obstruction in the ducts, as is shewn by a specimen of Dr. Hale White's in Guy's Museum, from a patient dying in the seventh week of enteric. Post-mortem examination shewed inflammation of the bile-passages within and outside the liver, together with cholecystitis. I do not think that influenza has been noted as a cause of suppurative cholangitis. I observed the connexion some time ago ; and the symptoms were so characteristic, and came on, in a lady of sixty-two, within so short a time of influenza, that I think there is every reason to believe this infection to have been the origin of the suppuration. Other similar cases have apparently confirmed the observation. The above-mentioned diseases are somewhat remote terms in the series of causation ; the immediate cause is the presence of pyrogenetic organisms within the biliary passages. The usual organisms are *B. coli* and staphylococci, but occasionally streptococci are present, in which case I believe that the issue is generally fatal.

Symptoms.—In suppurative cholangitis there is usually progressive enlargement of the whole liver, which may descend as low as the umbilicus ; the swelling being uniform, smooth, and tender to pressure. If the cause be in the common duct, and the gall-bladder has not previously become contracted, there will be the additional enlargement caused by its distension ; but when contraction of the gall-bladder has taken place, and also when the obstruction is in the hepatic duct, there will be no signs of cholecystitis. Pain may be entirely absent, as in one case on which I operated, in which the disease was dependent on cancer of the common duct ; but when the cause is gall-stones, the pain is usually severe and paroxysmal, each attack being accompanied by ague-like seizures and an intensification of the jaundice. In some cases, even when due to gall-stones, the pain may be so insignificant that the patient forgets it almost immediately and fails to mention it in his history. Jaundice is always present, and is usually both persistent and intense ; though where the obstruction is a floating gall-stone, acting like a ball-valve in the common duct, the jaundice may vary from time to time, or may almost disappear, so that the only sign may be a slight icteric tinge in the conjunctivae. Fever, with rigors and profuse perspiration, is a prominent feature of the disease, and rapid loss of flesh and strength likewise. The disease is always serious, and often proves fatal ; though, if the cause can be removed at an early stage, recovery may occur.

If the course be subacute the inflammation may concentrate itself in some part of the liver and lead to abscess ; in this case a distinct tender swelling may form and give rise to the usual symptoms and signs of hepatic abscess. If ordinary infective cholangitis pass on to general suppurative cholangitis recovery is improbable, especially if the infection be streptococcic. Hepatitis and multiple liver abscesses frequently follow cholangitis, and are usually followed by general and fatal infection of the system. Pneumonia and pleurisy ending in empyema are serious and

not infrequent complications. Endocarditis at times occurs, and as it has been known to follow cholangitis with hepatitis, and cholangitis without abscess, this cause should never be lost sight of in any case of infective endocarditis. In these cases the bacterium in the vegetations on the inflamed endocardium has been found to be identical with that discovered in the infected bile. Jaccoud and Aubert have also found endocarditis in cases of cholangitis.

As the pancreatic ducts frequently participate in inflammation of the bile-ducts, it not infrequently occurs that suppurative pancreatic catarrh or abscess of the pancreas may complicate both infective and suppurative cholangitis. (*Vide* 5, 6, 8.)

Treatment.—Unless free evacuation of the infected contents of the bile-passages can be accomplished, either naturally or artificially, treatment is virtually useless. If practicable, choledochotomy, with removal of the cause, should therefore be performed, and free drainage established and continued until the bile is sterile, or nearly so. Although good results cannot be expected in all cases, an amelioration of the symptoms may be looked for in some, and complete relief in others.

If a localised abscess be discovered in the liver, it should be opened and drained, and though in these serious cases it is scarcely to be expected that operation can be always successful, the chance of permanent benefit is worth snatching at, even under the most desperate conditions. Of general means, warm applications to the hepatic region, an initial mercurial purge followed by milder saline laxatives, intestinal antisepsis by bismuth and salol, the relief of pain by sedatives if called for, and the treatment of symptoms as they arise, will afford some amelioration, though the relief will probably be but temporary.

On drainage of the gall-bladder or common duct a certain number of important therapeutic results follow. (i.) The infective contents of the gall-bladder are evacuated; (ii.) calculi, which are frequently present, are removed; (iii.) the other biliary passages, more or less obstructed either by calculi or by swelling of their walls, are rendered as free as possible; (iv.) the infective bile is allowed to escape and mechanically washes out the lower passages, carrying away through the drainage-tube many of the infectious elements; (v.) the relief of pressure prevents absorption of the septic elements; (vi.) the relief to the kidneys, by allowing the bile to escape freely, is also of importance; as they are thus enabled to perform their function more freely in relieving the system of septic and other materials.

Terrier narrates several cases in the utmost detail, an account especially interesting, as he describes the bacteriological examination of the discharge from the fistula at different dates, and conclusively shews the gradual diminution in the virulence of the discharge after some days' drainage, and points to the need of rather more prolonged drainage than some of us have been wont to employ; until, indeed, the bacteriological examination of the discharge shews it to be sterile, or nearly so.

Ulceration, Perforation, Fistula, and Stricture.—These pathological

conditions may conveniently be considered together, as they usually, though not constantly, own one origin, namely, gall-stones ; moreover, perforation, fistula, and stricture are all accompanied or preceded by ulceration.

5. Ulceration of the gall-bladder and bile-ducts is found to be present in many cases of impacted gall-stone ; and it doubtless helps to explain the infective symptoms which are present in some cases of cholelithiasis and absent from others. Ulceration is generally found also where gall-stones have led to empyema of the gall-bladder or to suppurative cholangitis. The ulcers may be quite superficial, mere abrasions of the epithelial lining, or they may be deeper, extending into or through the other coats. Ulceration is, however, chiefly important from its effects—perforation, fistula, or stricture. Ulceration, or even perforation of the gall-bladder or bile-ducts, may occur independently of gall-stones. Dr. Hale White described a fatal case of enteric fever in a boy of seventeen, in which there were, besides the usual signs of the fever in the intestine, suppuration and ulceration in the gall-bladder, though there was no obstruction to the passage of bile. In some places the walls of the gall-bladder were very thin and almost perforated. Murchison says : "The lining membrane of the gall-bladder is very liable to become inflamed in enteric fever without producing very marked symptoms during life" ; later, he refers to a case of death from perforating ulcer of the gall-bladder in a youth aged nineteen on the fifteenth day of enteric fever. Perforation of the bile-passages is not uncommon, but general peritonitis from this cause is rare ; as the ulcer advances, extravasation is prevented by adhesive peritonitis. General suppurative peritonitis from perforation does, however, occasionally occur, leading to a sudden peritoneal catastrophe and, as a rule, to a speedily fatal termination, unless operation be performed within a few hours. In cases of rupture of the gall-bladder from straining, as in cases reported by Willard and by Mr. Lane, there was in all probability some previous disease, such as ulceration, leading to thinning and weakening of the walls of the gall-bladder, and disposing to rupture from slight causes. George P. Biggs reports a fatal case of perforating ulcer in a woman who had suffered a month previously from gall-stone colic. The onset was sudden, and was accompanied by cramp-like pains in the upper abdomen, which were rapidly followed by signs of acute general peritonitis. She died on the fourth day of illness. At the autopsy the abdomen was found greatly distended and full of a dark-brown, bile-stained fluid having a slightly faecal odour ; the peritoneum was covered with fibrinous exudation. Just inside the orifice of the common bile-duct a large gall-stone was impacted, and at the junction of the gall-bladder and cystic duct a minute oblique perforation was found in the floor of an old ulcer. The cystic, hepatic, and common ducts were all much dilated, the latter admitting a cylinder one centimetre in diameter. The muscular wall of the gall-bladder was hypertrophied, and the mucous membrane thickened from chronic inflammation ; near the outlet there was superficial ulceration.

6. If perforation be recognised and operated on at once, recovery is possible—as in the case of a man aged forty-five, whom I saw with Dr. Braithwaite of Leeds, and who, after symptoms of inflammation in the hepatic region extending over several weeks, suddenly became worse and shewed signs of general peritonitis. I opened the abdomen in the right linea semilunaris and evacuated several pints of bile and pus. The abdomen was washed out, and drainage-tubes were passed, between the liver and diaphragm, into the right kidney pouch and downwards towards the pelvis ; the patient recovered and is now in perfect health. I have since operated successfully on several cases of perforative peritonitis due to gall-stones. An interesting case of perforation of the gall-bladder following typhoid ulceration, successfully treated by abdominal section, was reported by Mr. Monier-Williams and Mr. Sheild.

In the greater number of cases perforation occurs slowly, as in a case of a feeble aged woman whom I saw with Dr. Chadwick of Leeds a few days before her death. Jaundice had been present for five years, and at the necropsy a large gall-stone was found lying in a cavity outside of the common duct, but pressing on it. The cavity was shut off from the general peritoneal cavity by adhesion of the neighbouring viscera. In some cases, as in one reported by Mr. Morton, the primary perforation may lead to the formation of a second cavity bounded by plastic lymph, which in its turn may rupture and lead to fatal peritonitis. The following is a brief account of the post-mortem appearance in the case referred to ; the patient was a woman of sixty :—“The body was well nourished, the abdomen was distended, and on opening it much orange-coloured fluid escaped, and general recent adhesive peritonitis was discovered. Just below the liver was a cavity the size of an orange, bounded above by the under surface of the liver, and in front by the thin margin of the liver and the omentum which had been adherent to it. Below, it was separated from the colon by much thickened tissue. On its inner side lay the omentum, and on its outer side, covered by adhesions between the liver and adjacent parts, lay the gall-bladder, which opened into the cavity by an aperture which would admit one or two fingers. The wall of the gall-bladder was much thickened, and several stones half an inch in diameter were found lying in it. Where the omentum had before been adherent to the anterior edge of the liver, forming the anterior wall of the cavity, it had become detached, and thus the bile had escaped into the peritoneum and set up fatal peritonitis. No doubt at one time the gall-bladder, containing gall-stones, had perforated under these surrounding adhesions, and thus the secondary gall-bladder had been formed, which in its turn had finally ruptured into the peritoneum. The old gall-bladder was not dilated to any extent.”

7. **Fistulas.**—A large gall-stone may ulcerate its way quietly, almost without symptoms, into the duodenum or colon, and produce no distress until in the intestinal canal, when all the symptoms of acute intestinal obstruction may result (*vide Vol. III. p. 743*). Rarely gall-stones have ulcerated their way into the pelvis of the right kidney and set up

symptoms of renal stone. I recently removed a gall-stone the size of a pullet's egg from the stomach of a man aged seventy, at the same time closing the gastric fistula and removing the gall-bladder. The patient recovered and is now well. He had had no symptoms up to three days before operation. Where adhesions form between the gall-bladder and the parietes an abscess may form in the abdominal wall, either over the region of the gall-bladder, at the umbilicus or elsewhere, which, on being opened, discharges pus and gall-stones, and leaves a fistula which, without further treatment, may become permanent, and discharge mucus or mucopus or bile; sometimes such a fistula may close spontaneously if the obstruction have passed away. Contrary to what one might suppose, fistulas between the bile-passages and other hollow viscera in the majority of cases close spontaneously, leaving visceral adhesions: thus intervisceral gall-bladder fistulas are but rarely found after death.

A fistula may at times open the way to septic absorption and to death from septic complications. Mucous fistulas are occasionally seen after the operation of cholecystotomy where the obstruction in the cystic duct has not been overcome, or where that duct is the seat of stricture. In one case of this kind with which I am acquainted, the patient has so little inconvenience that she does not think it worth while to undergo any further treatment. In other cases of mucous fistula dependent on stricture of the cystic duct I have removed the gall-bladder, effecting thereby a complete and permanent cure.

Biliary fistula may also continue after cholecystotomy where the common duct is strictured, or where the obstruction is permanent, or has not been removed. In cases of this kind, dependent on stricture, I have connected the gall-bladder to the intestine by the operation of cholecystenterostomy and then closed the external wound; thus curing the fistula and restoring the flow of bile to the bowel with completely satisfactory results.

8. Stricture is probably always the result of ulceration due to gall-stones, and may not manifest itself until the original cause has passed away. If in the cystic duct, it leads to a gradual and almost painless distension of the gall-bladder; if in the hepatic duct, to a gradual increasing jaundice with enlargement of the liver, but without distension of the gall-bladder; if in the common duct, to jaundice, enlargement of the liver, and distended gall-bladder; though if the stricture have been caused by gall-stones in the common duct the gall-bladder may be contracted. In one such case on which I operated, the history of gall-stones had extended over a period of eighteen years, and for three years there had been persistent jaundice dependent on stricture of the common bile-duct.

The first and last events are not very uncommon, as will be gathered from the foregoing remarks; but stricture of the hepatic duct independent of growth is probably very rare, though a fatal case has been reported.

Stricture may be found occasionally in the middle of the gall-bladder producing an hour-glass contraction of that ordinarily pear-shaped cavity.

In one case I found the upper cavity separated from the lower by a stricture apparently impermeable ; both cavities contained gall-stones which were successfully removed.

Needless to say, stricture of the bile-passages will scarcely call for diagnosis apart from its cause ; though different treatment will be demanded when the disease is recognised at the time of operation.

In stricture of the cystic duct the gall-bladder should be removed, otherwise the symptoms will recur when the wound closes, or there will be a permanent mucous fistula. Or the gall-bladder may be "short-circuited" into the intestine, as in the remarkable case reported by Mr. Swain. In stricture of the common duct cholecystenterostomy must be performed, not a simple cholecystotomy ; otherwise a permanent biliary fistula will certainly be formed. In certain cases of simple stricture of the common duct it may be possible to divide the stricture longitudinally, and suture the incision transversely, thus abolishing the narrowing of the passage, as in the operation of pyloroplasty.

9. Acute Phlegmonous Cholecystitis and Gangrene.—Acute phlegmonous inflammation of the gall-bladder was described by Courvoisier in 1890 under the name of acute progressive empyema of the gall-bladder ; and he stated that it usually leads to a fatal termination in a few days from diffuse peritonitis. Only seven cases are recorded in Courvoisier's voluminous statistics. Potain also says that, besides the ordinary variety of empyema of the gall-bladder, there is an acute empyema of a very grave kind, which is followed by rapid peritonitis and death. In one case, which he describes, death occurred on the second day after the onset of the attack ; and although there was no perforation of the walls of the viscus, infection had spread through the coats to the general peritoneal cavity. From the large number of cases that I have treated the disease is evidently not uncommon. In 1906 I published a series of fifty-seven cases of removal of the gall-bladder (41), which has now been extended to nearly a hundred.

Although the disease is usually associated with gall-stones, Mr. Lane's and some of my cases would seem to prove that acute cholecystitis may arise independently of them. Enteric fever may give rise to it, as in the case recorded by Mr. Monier-Williams and Mr. Sheild.

Whatever be the cause, acute phlegmonous cholecystitis usually appears somewhat suddenly with pain on the right side of the abdomen, which rapidly becomes general. A rapid and feeble pulse, quick thoracic breathing, fever, intense general depression, marked tenderness, especially over the right side of the abdomen, rapidly increasing tympanites, persistent vomiting, and an extremely anxious expression of countenance, are its chief symptoms. The acute peritonitis, significant of the disease, may be localised at first ; but later it becomes general. Jaundice may or may not be present ; and although an elevation of temperature is usual, it is by no means constant, and affords but slight assistance in diagnosis or prognosis. If the disease be of the very acute or gangrenous variety, death speedily occurs ; but if of the subacute form, an abscess may form round the gall-

bladder, and the peritonitis may become localised ; the disease then resembles a perityphilitic abscess in its course.

The diagnosis of phlegmonous cholecystitis practically resolves itself into a diagnosis of the cause of an acute peritonitis starting on the right side of the abdomen. Although this may be due to perforation of the stomach at or near the pylorus, to perforation of the duodenum or ascending colon, to perforation of the gall-bladder or bile-ducts, or to some other such peritoneal catastrophe, the chief affection with which it is likely to be confounded is acute appendicitis. In appendicitis the pain begins at a lower point in the abdomen and passes towards the umbilicus, whereas in gall-bladder mischief it begins below the right costal margin, and passes towards the epigastrium and back to the right scapular region. In the one case the most acutely tender spot is over the caecum ; in the other it is over the region of the gall-bladder. The symptoms of acute peritonitis and paralytic obstruction of the bowels are common to both. The appendix may be abnormally situated under the right costal arch and so give rise to a difficulty in diagnosis, as in a case I operated on in which a suppurating appendix was adherent to the gall-bladder and liver. Fortunately, the treatment by exploratory incision is that appropriate to any one of the various conditions mentioned.

Treatment.—Relief of pain by injections of morphine will probably always be demanded as a primary measure ; and as it is clearly impossible to make a diagnosis of this serious malady within the first few hours, warm applications, absolute rest, the stoppage of feeding by the mouth (unless it be in very small quantities), and the relief of symptoms as they arise, must be our temporary measures ; but as soon as the diagnosis of phlegmonous cholecystitis can be established, and it is found that the patient is getting worse rather than better, an exploratory incision should be made, and the gall-bladder incised and drained, or better, completely removed by cholecystectomy, the cause, if any obvious one be found, being then removed. If, however, gangrene be discovered, the gall-bladder should undoubtedly be removed, the indications for that measure being as distinct as in the case of a gangrenous veriform appendix. If, in subacute cases, the inflammation becomes localised, and a swelling with tenderness be found beneath the right costal margin, incision and drainage are called for ; at the same time cholecystotomy may be performed, and if gall-stones be present in the gall-bladder or ducts they may be removed. If the patient be too ill to bear a prolonged operation the latter procedure may be left to a subsequent occasion.

Gangrene.—The comparative frequency of gangrene in the veriform appendix might lead one to suppose that gangrenous inflammation of the gall-bladder would not be uncommon ; yet it is only occasionally seen. So far as I know, L. W. Hotchkiss' case was the first recorded. In this case, a boy, aged nineteen, was admitted to the Bellevue Hospital, New York, with acute peritonitis ; it had come on suddenly and was thought to be due to appendicitis, as the pain was most severe over the caecal region. No previous history of gall-stones was obtainable.

Exploration of the abdomen revealed a tumour of purplish hue, very tense and markedly congested; some pus was found on its outer side, and, within it, thin, sticky fluid of a yellowish-brown colour, together with a number of gall-stones. The lower end of the gall-bladder was almost black; its walls were extremely thin and apparently gangrenous. Death occurred seven hours after the operation—thirty-four hours after the onset of the attack; the vomiting, rapid pulse, and high temperature continuing to the end. I have operated successfully by cholecystectomy on several cases in which acute phlegmonous cholecystitis was passing into or had actually ended in gangrene. In one of the cases no gall-stones were found, though in others cholelithiasis was the manifest exciting cause.

In order to explain the occurrence of gangrene three factors have to be borne in mind: (a) thrombosis of the nutrient vessels; (b) bacterial infection; (c) absence of drainage and consequent tension. The two latter are present in both gall-bladder and appendix inflammation; but the first factor is more frequent in the vermiciform appendix, which is supplied by one nutrient artery only; whereas the gall-bladder has a very free blood-supply, not only through the branches of the cystic artery, but also through their anastomoses with the hepatic, where the organ is fixed to the liver. In Hotchkiss' case there was an abnormal circular constriction of the gall-bladder with lymph infiltration, which was apparently sufficient to cut off the blood-supply from the extremity of the part.

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TUMOURS OF THE GALL-BLADDER AND BILE-DUCTS.—If by tumour be understood new growth, then tumours of the gall-bladder and bile-ducts are not common; but if we accept the usual interpretation of the word, and call all enlargements tumours, we shall find them by no means rare. The greater number depend directly or indirectly on gall-stones.

The following classification includes the chief tumours of the gall-bladder and bile-ducts:—

I. Tumours of the Gall-bladder.

A. Distension : (a) with bile ; (b) with gall-stones ; (c) with mucus, hydrops ; (d) with pus, empyema ; (e) with air.

B. New growths. (a) Malignant ; (b) non-Malignant.

II. Tumours of the Bile-ducts.

A. Distension.

B. New growths. (a) Malignant ; (b) non-Malignant.

I. **Tumours of the Gall-bladder.**—*Etiology.*—The gall-bladder may become hard and almost calcified by the deposit of lime salts in its walls in consequence of disease of its mucous membrane. Usually it can then be felt under the liver margin as a hard nodule, though it seldom forms a tumour of any size. Though a considerable collection of gall-stones, or one large concretion contained in the gall-bladder, may cause a palpable tumour, this is rare; the swelling, as a rule, is due to distension of the gall-bladder in consequence of an obstruction of the lumen of the ducts by gall-stones, so that the escape of the secretions is prevented. If a gall-stone, in passing down the cystic duct, become impacted, so as to block the passage, the gall-bladder gradually becomes distended with mucus, and a tumour is formed. If a concretion be impacted in the common duct the gall-bladder may be distended with bile for a short time, though if the obstruction continue, mucus will take the place of the bile.

Stricture or tumour of the cystic or of the common duct or interstitial pancreatitis may produce distension of the gall-bladder; so also may hydatid disease, movable kidney and malignant growth lying outside the bile-ducts but pressing on them.

If the symptoms be acute and associated with inflammation, the contents of the gall-bladder may become purulent and a so-called empyema be formed. In certain cases of empyema the size of the tumour may be increased by the formation of pus outside the gall-bladder. The pus may then lie in an irregular cavity either in the liver or below it, but shut off by adhesions from the general peritoneal cavity.

Of the tumours dependent on new growth, "cancer" of the gall-bladder is the most important; innocent growths, except of inflammatory origin, are excessively rare. I reported a case of adenoma of the gall-

bladder successfully removed by cholecystectomy, and a tumour of the gall-bladder due to actinomycosis, which was cured by curettage and drainage, with the subsequent administration of iodide of potassium (50).

Cancer of the head of the pancreas is usually associated with a perceptible tumour of the gall-bladder, as the new growth embraces and obstructs the termination of the common duct and thus causes retention of secretions.

Signs.—Enlargements of the gall-bladder may vary from a tumour just perceptible to the touch to one of such a size that it may resemble an ovarian cyst, as in cases reported by Terrier and Lawson Tait; though an enlargement of greater size than a large pear is exceptional. The same tumour may also vary in size at different times—a variation frequently found in gall-stone obstructions. The symptoms of tumour of the gall-bladder depend for the most part on the cause, and consequently vary considerably—being at times slight and unimportant, at times both urgent and serious. The gall-bladder as a rule enlarges downwards and forwards in a line which, drawn from the ninth or tenth costal cartilage, crosses the linea alba a little below the umbilicus; but the position of the tumour varies with the size of the liver. When this organ is of normal size the neck of the gall-bladder is opposite the ninth costal cartilage; whereas when the liver is enlarged the gall-bladder will be pushed down so that the neck of the tumour may be opposite to the umbilicus, or even below it. If uncomplicated it will have a smooth, rounded, and pear-shaped outline, the larger end below being quite free and movable from side to side, the upper end being fixed and passing under the lower margin of the liver at the fissure of the gall-bladder. A distinct sulcus between the liver and gall-bladder is nearly always perceptible to the touch: if the warm, flat hand be laid over the right side of the abdomen, and the patient be told to take a deep breath, the tumour and the liver will descend together and pass under the fingers.

Bimanual palpation will frequently throw additional light on the case: the right hand is to be placed in front of the abdomen, and the left under the right loin, and gentle pressure made forwards. In other cases additional information may be obtained by placing the patient in the genu-pectoral position, and passing the flat hands round the abdomen from behind, when a tumour of the gall-bladder will rest directly on the hands; on deep inspiration it will be felt to move just beneath the abdominal walls: the upper surface of the liver is also capable of palpation in this way. The sac, as a rule, is far too tense for fluctuation to be felt, though at times, when it is less tense, this sign may be obtained. In some of the larger swellings a thrill, almost like the hydatid fremitus, may be felt on gently flicking the tumour with the finger-nail. Percussion by no means always discovers dulness coextensive with the tumour, and is especially deceptive if the surrounding intestines be distended: dulness on percussion is therefore a very variable sign; palpation will be found more trustworthy. Inspection of the abdomen, with the patient recumbent, will at times shew the tumour descending on respiration; but

this sign is usually to be observed only in thin patients and in cases uncomplicated with inflammation. When there is inflammation and matting of the adjoining viscera, a fixed swelling, dull on percussion and decidedly tender, may be seen over the right hypochondrium. Tenderness on palpation is a variable symptom, depending on the presence or absence of local peritonitis ; as a rule it is absent in uncomplicated enlargements of the gall-bladder.

Jaundice may accompany tumours of the gall-bladder, both being dependent on the same cause—the blocking of the common bile-duct. Although not absolutely pathognomonic of malignant disease, the combination should always arouse a suspicion of cancer of the head of the pancreas, or of the liver or bile-ducts, especially if it be associated with great loss of flesh and strength, and with absence of characteristic gall-stone pain. In a considerable number of cases I have observed distension of the gall-bladder with jaundice to be associated with malignant disease ; but much less often the combination of tumour, jaundice, and gall-stones. The explanation of this apparent anomaly is that the gall-bladder frequently becomes diminished in size as the result of gall-stone irritation, so that when the common duct becomes blocked by a stone jaundice occurs, but the previously shrunken gall-bladder is unable to expand. This is often spoken of as Courvoisier's law. If, however, the common duct become blocked by gall-stones before the gall-bladder has contracted and formed adhesions, the combination of jaundice and tumour may occur. If, when the common duct is blocked by a new growth, the gall-bladder has not been subjected to previous irritation, and has not therefore become contracted, it will dilate at once. Thus, in malignant disease of the head of the pancreas we usually find the combination of jaundice with tumour of the gall-bladder (*vide p. 306*).

Gall-bladder tumours usually contain mucus, occasionally pus, rarely bile. In all cases of obstruction of the cystic duct in which inflammation has not followed, mucus alone is present ; though, when inflammation coexists, pus or mucopus may be found. In obstruction of the common duct by gall-stones, the gall-bladder, though usually contracted, may be found distended by bile at first and by mucus later. As a rule, however, the swelling subsides more or less rapidly, the gall-bladder shrinks, and no tumour persists. When the obstruction becomes absolute, as in malignant disease of the head of the pancreas, the tumour formed is persistent ; and although the block is in the common duct, bile soon ceases to reach the gall-bladder, and the tumour is always found to contain mucus only.

In one case, not previously reported, I found a gall-bladder tumour to contain gas. The patient gave a history of gall-stones years previously, and shewed several large ones that had caused intestinal obstruction, but which had ultimately passed through the anus. After years of relief, pain recurred associated with symptoms of infection and the presence of a tumour resonant on percussion. A fistula between the gall-bladder and the duodenum was diagnosed, and at operation a communication was found

between the gall-bladder and duodenum large enough to admit gas and to infect the gall-bladder, but too small to permit of free drainage. Cholecystectomy and repair of the duodenal opening was followed by perfect recovery. In a case of pyopneumocholecystitis in which there was a communication with the colon the gall-bladder formed a large tympanitic tumour (Pende).

Diagnosis.—Tumours of the gall-bladder may have to be distinguished from—(a) movable right kidney, (b) tumour of the right kidney or of the suprarenal, (c) tumour of intestine or faecal impaction, (d) tumour of liver, (e) pyloric tumour, (f) abnormal projection of liver. The diagnosis of enlargement of the gall-bladder from movable right kidney in thin persons is as a rule easy, but in those who are stout, or have tense or strong muscular abdominal walls, difficulties may and do arise which, however, can usually be overcome by examination under an anaesthetic.

These enlargements resemble one another in that they form moderate-sized, distinctly defined, smooth, rounded, and movable tumours on the right side of the abdomen, which descend on inspiration. The previous history may throw light on the individual case, especially if there have been definite gall-stone attacks or jaundice. By inspection of the abdomen a gall-bladder tumour is often apparent, moving rhythmically with the respiratory movements when the patient is recumbent; a floating kidney can rarely be so detected. The general outline of the tumour, as detected by palpation, may afford valuable assistance; thus, in distension of the gall-bladder, the tumour formed is pear-shaped, with the apex towards the fissure of the gall-bladder, and its long axis in a line from about the tip of the ninth costal cartilage downwards, forwards, and inwards towards a point a little below the umbilicus. In floating kidney, especially in patients with lax abdominal walls, the tumour may be grasped and its characteristic shape made evident. Should adhesive peritonitis accompany the gall-bladder condition there will be tenderness and pain on pressure over the tumour, especially near its apex. These signs are rarely if ever present in floating kidney. The gall-bladder tumour on manipulation can usually be moved to a limited extent inwards and outwards; but in no circumstances can it be depressed into the pelvis. On relieving the pressure it tends to resume its old position under the liver. Floating kidney generally has a wider movement; it can be depressed towards the pelvis, and, when relieved of pressure, it tends to pass towards the right loin, especially when the patient is recumbent. A valuable diagnostic sign is the sulcus often felt between the lower margin of the liver and the gall-bladder tumour. This can usually be felt when the warm flat hand is placed over the upper part of the swelling, and the patient breathes deeply.

In the case of renal tumour, as well as in movable kidney, distension of the intestine with air will press the kidney back into the loin; but the gall-bladder will be pushed up towards the liver and made more prominent. The last test is usually also sufficient to enable a

diagnosis to be made between a distended gall-bladder and a tumour of the right suprarenal body; but this point is not always to be relied upon. In one case this test of Ziemssen's pushed the swelling upwards; and on performing abdominal section, a malignant suprarenal growth was found and removed. The explanation was that the colon was fixed below the growth and pushed it up when the bowel was distended.

In tumour of the intestine or of the pylorus the associated symptoms are usually sufficient to enable a diagnosis to be made; but, when in doubt, distension of the stomach or bowel with gas, or examination under an anaesthetic, will be of assistance. Tumour of the liver itself—whether cancer or hydatid disease—may be almost indistinguishable from one of the gall-bladder; though the presence of nodules in the liver, with the history and other symptoms of malignant disease, will usually be sufficiently distinctive in cancer, whilst the less localised and more generally fluctuating swelling, together with the longer history and absence of pain, will distinguish hydatid tumour. It should not be forgotten that the right lobe of the liver may have an abnormal projection either in the site of the gall-bladder or to the right of that position, and may thus at first be mistaken for an enlarged gall-bladder; but the absence of symptoms, together with careful bimanual palpation, will usually enable a correct diagnosis to be made, and, as Riedel has pointed out, the gall-bladder may frequently be felt apart from the swelling. A Riedel's lobe is wider above, whereas a distended gall-bladder narrows upwards and usually leaves a sulcus between itself and the liver. Puncture with an exploring syringe would, of course, give valuable information; but, as this measure is not devoid of risk, it should not be lightly undertaken; death has occurred on more than one occasion as a direct result of this apparently slight operative procedure. If it be decided to employ an exploring needle, the aspirator should always be used in order that the tense cyst may be emptied; otherwise leakage from the puncture is almost certain to occur. In cases of doubt, especially where the symptoms demand interference, exploration of the tumour through a small abdominal incision can be undertaken with very little risk; and further treatment, if called for, can be readily carried out at the same time.

Cancer of the gall-bladder is by no means frequent, and as a primary affection is somewhat rare. Fütterer (44) collected 268 cases, of which no less than 195 has been reported since 1880. It is usually due to the irritation of gall-stones or to extension from adjoining organs, and in the latter case it is hardly amenable to surgical treatment. The growth is usually a cylindrical-celled carcinoma, but may be spheroidal-celled or shew a transition between those two forms. In one of my cases, in which cholecystectomy was successfully performed, the disease proved to be squamous-celled carcinoma, and Fütterer (45) has since collected 13 examples of this form of carcinoma. About 10 cases of primary sarcoma are on record. The disease occurs as a uniform thickening of the walls of the gall-bladder, and in the centre of the mass a

cavity containing gall-stones is often found. It may attain the size of a large pear.

Predisposing Cause.—No less than 73·2 per cent of cases of cancer of the gall-bladder and bile-ducts on which I have operated were associated with gall-stones. Zenker found gall-stones in 85 per cent of cases of cancer of the gall-bladder, Musser in 69 per cent, and Courvoisier in 88 per cent. These figures establish undoubtedly a relationship between cholelithiasis and cancer of the bile-passages, and as gall-stones can be removed in the early stages before serious complications supervene, with hardly any risk (in my experience in a large number of cases not 1 per cent), the preventive treatment for cancer of the gall-bladder and bile-ducts is obviously removal of the cause.

Symptoms and Signs.—If the growth be primary, there will be the history of a more or less rapidly growing tumour appearing under the right costal margin; it is accompanied by a sense of discomfort, shortly changing to pain, which is often worse at night, and which, though at first localised to the right hypochondrium and epigastrium, usually extends round the side to the right infrascapular region. When the enlargement is first noticed, it is felt as an egg-shaped swelling beneath the liver, descending with that viscus on inspiration. The tumour is hard to the touch, and very slightly or not at all tender to pressure. At a later stage it becomes more fixed and more diffuse, and nodules may form and be felt on its surface. As the growth extends, it invades the liver and sometimes the duodenum and stomach.

Dissemination is rare. When it occurs, nodules may be found in the liver, and generally over the peritoneum; in such cases ascites appears. The lymph-glands in the hilum of the liver usually become affected. As the hepatic or the common bile-ducts are or are not invaded, so will be the presence or absence of jaundice; but in nearly half of the cases some degree of icterus will be found as the disease advances. Interference with the action of the bowels, even to partial or complete obstruction, occurs at times. General failure of health, continued wasting with loss of strength, ascites, and marked cachexia characterise the later stages. If gall-stones be present there will be the usual antecedent history of cholelithiasis. I have known the combination of gall-stones and cancer of the gall-bladder to be unaccompanied by jaundice. Where gall-stones with jaundice complicate cancer of the gall-bladder, exacerbations of pain will usually be accompanied by rigors, fever ("ague-like attacks"), and an intensification of the icterus; moreover, in such cases petechiae in the skin and haemorrhage from the nose and rectum usually appear.

Diagnosis.—Cancer of the gall-bladder may usually be diagnosed by the progressive character of the disease, and by the presence of the characteristic hard tumour; but it is by no means always easy to diagnose cancer from a tumour formed by matted intestines, due to local peritonitis near the gall-bladder.

In a doubtful case of this kind, in a woman of fifty, I opened the

abdomen, and found what appeared to be a malignant tumour of the gall-bladder, which was punctured in several spots with an exploring syringe. Finding it firm and hard I concluded it was malignant, and as it was too extensive for removal I closed the abdomen, thinking nothing more could be done. The patient, however, recovered forthwith, is now well, and has no remnant of her tumour. In all probability it was an inflammatory swelling associated with gall-stones. In another case of tumour, in which there was a suspicion of malignancy, an abscess of the liver, containing thirty gall-stones, was opened, with marked relief, though only for a time; death supervened four months later, when cancer was found. When in doubt exploration is advisable, as treatment may be carried out at the same time.

Malignant disease of the right suprarenal body may afford a difficulty in diagnosis. The same difficulty applies to cancer of the pylorus, which, however, is accompanied for the most part by characteristic stomach symptoms.

Treatment.—The alleviation of symptoms, especially of pain by sedatives, is practically all that can be done, except in those rare cases in which the disease is limited to the gall-bladder, when cholecystectomy may be performed. That cholecystectomy is occasionally practicable in cancer of the gall-bladder, is proved by a case reported in June 1896, in which I had removed from a middle-aged woman not only the whole of the gall-bladder but a considerable portion of the adjoining right lobe of the liver also; the patient made a good recovery. The disease had started at the neck of the gall-bladder behind an impacted gall-stone. Microscopic examination shewed the growth to be a squamous-celled carcinoma. Since then I have performed cholecystectomy for cancer on several occasions with success (48). In one case operated on in August 1900, the removal of the gall-bladder, pylorus, and a portion of the liver was followed by recovery, and the patient was well six years later. Microscopically the tumour was a carcinoma. Another patient was well seven years later.

II. Tumours of the bile-duets rarely form projections so large as to be distinguished through the abdominal walls. Tumour, however, in such cases, as a rule, is present sooner or later on account of the obstruction in the ducts and secondary distension of the gall-bladder; or if the gall-bladder be contracted, the common duct may become so dilated as to form a cystic tumour with all the characteristics of a distended gall-bladder. Mathieu has collected 20 examples of large cysts of the common bile-duct.

Terrier describes four cases in which an external fistulous opening was established from the common bile-duct. In three of these the duct was much distended, and formed a distinct abdominal tumour. The first case was one in which median laparotomy was performed for the removal of a swelling regarded as a cyst of the pancreas. The nature of this swelling having been revealed by the discharge of bile after puncture, a small portion of the wall of the cyst was excised, and the edges of this

opening were attached to the external wound. The biliary fistula thus formed bled freely for some days after the operation, and afterwards suppurred. The patient died on the twenty-ninth day from anaemia and exhaustion. In the second case the much-distended duct, which had been regarded as a hydatid cyst of the liver, was exposed by laparotomy, incised, and attached to the wound in the abdominal wall. The patient died on the eighth day from collapse. In the third case the dilated duct was opened and stitched to the external wound under the supposition that the tumour was a distended gall-bladder. In the original report of the fourth case it is not clearly stated whether the duct was distended or not. In this instance the hepatic portion of the divided duct was fixed to the surface of the abdominal wall, after removal of the gall-bladder, the cystic duct, and a small portion of the liver for cancer. The patient did well for some time after the operation, but died six weeks later from cachexia. In his comments on these records, Terrier points out that in two of the cases the distension of the bile-duct, though clearly due to obstruction, was not associated with lithiasis. In the third case the duct was found completely obstructed at its intestinal orifice by a small calculus. In all these cases the gall-bladder was much shrunken, and its walls were sclerosed and surrounded by cicatricial tissue.

The following new growths have been found primarily in the bile-ducts : (a) Cylindrical-celled carcinoma ; (b) Papilloma. This is probably an earlier stage of carcinoma, and is rare. Sir W. Bennett removed one from the common duct of a woman in St. George's Hospital ; the specimen was shewn at the Pathological Society of London in May 1894 (53). The growth was white and somewhat granular to the naked eye, and it was in immediate relation with an impacted gall-stone. Microscopically it resembled a glandular polypus of the intestine. The papilloma was apparently due to the irritation of a gall-stone, which from the history appeared to have been impacted for two months ; (c) Adenoma. The intrahepatic ducts may shew multiple adenomas, or there may be a single adenoma which may become cystic and sufficiently large to imitate an ovarian cyst ; (d) A unique case of a primary melanotic sarcoma of the common bile-duct has been recorded by Duval.

Carcinoma, in most if not in all cases, is secondary to gall-stones ; though, as in a case on which I operated (47), they are not always found, as the stones may have passed into the bowel before the operation. Dr. H. D. Rolleston (52) found gall-stones present in 37 per cent of all cases of cancer of the bile-ducts that he examined. Although these tumours are usually in the common duct, they may occur in the cystic or in the hepatic duct. If forming in the cystic duct, jaundice will be absent at first, coming on later when the growth advances so far as to press on the common duct and obstruct the passage of the bile. The gall-bladder enlarges at an early stage, and this will probably be the first sign ; pain may be absent unless gall-stones exist, when the usual spasmodic pain will occur so long as the muscular coat of the gall-bladder retains its contractile power. When the growth

is in the common duct jaundice comes on at an early stage, and persists throughout, the liver gradually increasing in size, and the gall-bladder also enlarging ultimately. Suppurative cholangitis is apt to supervene, in which case the course is more acute, and is accompanied by fever, ague-like attacks, and rapid loss of flesh and strength. If the tumour form in the hepatic duct, jaundice will be the earliest symptom, and the case will resemble one of obstruction in the common duct, except in the absence of enlargement of the gall-bladder. Needless to say, the disease is uniformly fatal, though operation may delay the final catastrophe. The growth is usually a cylindrical-celled carcinoma.

Besides primary carcinoma of the bile-ducts, malignant disease may invade them, by direct continuity, from the gall-bladder, from the pancreas, or from the liver; the symptoms are then those of growth of the bile-ducts engrafted on the original disease.

The diagnosis of cancer from gall-stones in the bile-ducts is difficult; the symptoms are similar, and in fact the two frequently coexist. The absence of pain and the rapid deterioration of health may afford a little help, but in some cases the pain is as acute as in cholelithiasis. A pathological investigation of the urine is of great assistance, for as a rule in common duct cholelithiasis there is associated catarrhal or interstitial pancreatitis, when Cammidge's reaction will shew characteristic crystals. A chemical examination of the faeces also affords help. In growth the obstruction to the bile-flow is often absolute, whereas in gall-stone in the common duct there is usually some bile passing and recognisable by chemical if not by visual investigation.

Cystic dilatations of the bile-ducts are indistinguishable from enlargements of the gall-bladder, for which indeed they are usually mistaken until the abdomen is opened.

The operative treatment of tumours depends both on the nature of the growth and on its site. I have mentioned above cases of removal of tumours of the gall-bladder, both malignant and non-malignant, by cholecystectomy, and when the growth is in the cystic duct, removal may be readily effected by the same operation. Any growth should be removed if possible; but, where this is impracticable, the dilated gall-bladder may be opened, stitched to the surface, and drained; or better still, it may be drained into the duodenum or jejunum by making an anastomosis by means of a Murphy's button. Although hitherto the results of choledochostomy for extreme cystic dilatation of the common duct have usually been fatal, probably because extreme distension of the bile-duct is often accompanied by infection of the biliary passages, it would be well to reserve our opinion on the prospects of the operation. As yet very little information can be obtained on this subject; cases of distension of the common bile-duct are very rare, and those in which surgery has intervened are still rarer. An extremely interesting case is reported by Mr. W. P. Swain, in which he connected a dilated bile-duct to the jejunum by one of Murphy's buttons. The size of the tumour, which occurred in a girl of seventeen and was associated with gall-stones,

may be gathered from the fact that over seven pints of fluid were withdrawn from it at the time of operation. Three months later the patient was progressing satisfactorily, save that the temperature rose occasionally, and that the button had not been passed. In one case I connected a cystic tumour of the common duct to the duodenum by means of sutures over a decalcified bone bobbin with complete success, and the patient, a lady of twenty-eight, was well three years later.

In operating, it is important to bear in mind that the cause of dilatation of the ducts may be a removable one, such as gall-stones; and if removal be practicable, that should be done.

In several cases a cancerous tumour of the common duct has been removed with immediate success, though recurrence has, I believe, taken place at no distant date in all the cases.

Primary carcinoma of the ampulla of Vater is described on p. 578, Volume III.

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GALL-STONES

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THE importance of this subject may be gathered from the fact that post-mortem records on Europeans of all ages and of both sexes prove that gall-stones are present in from 5 to 12 per cent. In Strasburg the record is 12 per cent (Schroeder), in Kiel 5 per cent, and in Manchester 4·4 per cent (Brockbank); but as these statistics are taken from hospital patients representing the working-classes, who are the least subject to gall-stones, the estimate is probably below the mark. On the other hand, in India, as in the East generally, gall-stones are said to be rare.

Pathology and Etiology.—Gall-stones, which, when small, are often spoken of as biliary sand, may vary from a concretion just perceptible to the naked eye up to a mass the size of a tennis ball, or even larger. They may be round, egg-shaped, barrel-shaped, elongated with pointed ends, or angular ; the surface being smooth, mammillated, or irregularly faceted. Gall-stones, when large, are usually single, but when small or moderate in size, several hundreds may be present ; for instance I have removed from one patient as many as 1500 ; and over 2000 have been removed at one operation. Their colour is variable ; in some cases it is white or grey, in others very dark, or even quite black ; the usual colour is a dark yellow or brown. In consistency they are ordinarily firm, but may without much difficulty be fractured by pressure between the thumb and forefinger, the fracture being crystalline ; but they may be as hard as a uric acid calculus, or as soft as half-set putty. The chief constituent of gall-stones is cholesterin, which always occurs in the crystalline form ; but bile pigments, bile salts, lime, mucus, degenerated epithelium, and, rarely, foreign bodies may enter into their composition. Margarate, stearate, and palmitate of lime, combined with mucus, usually form the cement which binds the cholesterin crystals together to form a concretion.

Gall-stones formed almost entirely of bile pigment may be seen. On two occasions I have found soft concretions of this nature in large numbers in the hepatic ducts within the liver, and on several occasions in the common duct and even in the gall-bladder. Since cholesterin is the chief constituent of gall-stones, our attention in considering their formation must be directed chiefly to the physiology of this monatomic alcohol, which occurs, normally, not only in the blood, but also in the various organs of the body.

Although cholesterin is always present in the bile in a proportion, according to different authors, varying from .045 to 1.18 per cent, very little is known of the processes which determine its existence. As there is no proof that the liver excretes cholesterin from the blood, or that it is a result of hepatic metabolism, we are driven to the conclusion that it is formed in the bile-ducts or gall-bladder ; and, as it is found in other passages lined by mucous membrane when there is no bile near, there is no reason to believe that it is formed from any constituent of the bile, but rather that it is a product of the epithelium of the bile-passages—that, in fact, it is a secretion of mucous membranes generally (*vide p. 62*). Why, when ordinarily present in all persons, cholesterin should form concretions in some and not in others, may be dependent on several causes ; possibly in some cases cholesterin occurs in positive excess, whilst in others there may be a diminution of the bile salts which should hold the cholesterin in solution, or it may even be precipitated from solution.

There is no doubt that catarrh of the mucous membrane of the bile-passages increases the amount of cholesterin present, and that the longer bile remains in the gall-bladder the more cholesterin it will contain. Anything, therefore, which causes stagnation of bile may dispose to gall-

stones ; on the other hand, whatever leads to a regular emptying of the bile-passages will tend to clear out such detritus as cast-off cells and incipient collections of cholesterol crystals and mucus, and thus to prevent the formation of gall-stones. Among the remoter causes we must consider age, sex, habits, dress, diet, diathetic conditions, and disease.

Age.—Although gall-stones may occur at any age, and even in the newly-born (Portal and Lieutaud), they are less often found under the ages of 25 or 30 ; Schroeder says that under the age of 20 the percentage is 2·4 ; from 20 to 30, 3·2 ; from 30 to 40, 11·5 ; from 40 to 50, 11·1 ; from 50 to 60, 9·9 ; and over 60, 25·2 per cent. Prof. G. F. Still collected no less than 20 cases of gall-stones occurring in children, ten of which were in infants.

Sex.—Gall-stones occur more frequently in women than in men ; Schroeder finds that in Germany they are found in 20 per cent of female and in 4·4 per cent of male necropsies. Out of 228 autopsies on women in the Manchester Royal Infirmary, Dr. Brockbank found 18, and out of 542 post-mortem examinations in men, 16 cases of gall-stones ; which gives 7·9 per cent in female and 2·9 per cent in male subjects.

Pregnancy would seem to be a factor in the causation of gall-stones, as, in a large series of cases, 90 per cent of women affected had been pregnant. The wearing of corsets, which tend to force down the front of the liver and to depress the fundus of the gall-bladder, is probably a distinct etiological factor, especially when combined with want of exercise.

Habits.—Want of exercise, whether from lethargy or from necessity, as in some forms of chronic heart disease, leads to stagnation of bile in the gall-bladder, and to the deposition of cholesterol ; since the gall-bladder is unaided in its expulsive efforts by the abdominal muscles.

Catarrh of the gall-bladder and bile-ducts probably acts as a cause in two ways ; in the first place, it leads to stagnation of bile by paresis of the muscular coats of the passages, and in the second place by increasing the amount of cholesterol present.

Diet.—The following data go far to prove that diet exercises a strong influence in the formation of gall-stones. It seems probable that free cholesterol in the bile-passages is due, in many cases, to the deficiency of the solvents of it in the bile ; these solvents being the glycocholate and taurocholate of sodium which arise from the metabolism of nitrogenous foods. If the supply of nitrogen in the food be limited, the bile salts will be diminished and cholesterol may be precipitated. This may serve to explain the presence of gall-stones in gouty persons who on account of the lithic diathesis limit their intake of nitrogen. The larger consumption of farinaceous food in Germany may also serve to explain the greater prevalence of gall-stones there than in England, where meat enters more extensively into the dietary. In diabetes, in which nitrogenous food is prescribed, gall-stones are rarely found. Thudichum in his work on gall-stones stated that he could not find any recorded instance of the discovery of gall-stones in the wild carnivora ; though on two occasions they have been found in the gall-bladders of domesticated carnivora.

On the other hand, Dr. Brockbank could find no evidence of their occurrence in wild herbivora, though at times they are found in domesticated horses, cattle and sheep, as well as in pigs. Moreover, in pampered dogs fed on farinaceous foods they are found occasionally. In man who is omnivorous they occur in from 5 to 12 per cent. It will thus be seen that in those who take an abundance of albuminous materials in their food, and in whom, therefore, the bile salts are in sufficient quantity, there is little tendency to the deposition of cholesterin; whereas when little albuminous food is taken, and the bile salts are presumably insufficient to hold the cholesterin in suspension, gall-stones form; this tendency is aided by insufficient exercise, as in stall-fed cattle, pampered dogs, and indolent men. The formation of some gall-stones containing lime may possibly be caused by drinking hard water, but this is by no means proved. An insufficiency of diluent drinks may possibly act as a cause, and I think I have found this to be a factor in some cases.

Infection.—The microbial origin of gall-stones was first suggested by Galippe in 1886, who found bacteria in biliary calculi. Welch in 1890 found the *B. coli* and *Staphylococcus pyogenes* in gall-stones, and Hanot in 1896 found typhoid bacilli. Gilbert, Dominici, and Fournier found *B. coli* in 23 out of 70 cases, and they performed experiments on animals which shewed that the *B. coli* and the *B. typhosus* are capable of setting up a cholecystitis which tends to the formation of gall-stones. Mignot succeeded in producing typical gall-stones in animals by the employment of attenuated virus. The varieties of the bacteria seem to be of secondary importance, for Mignot proved that *B. typhosus*, *B. coli*, staphylococci, streptococci, and even *B. subtilis* were capable of giving rise to calculi. In many of my own cases a clear history of enteric fever was obtained some months before the first symptoms of cholelithiasis, and I believe that I have traced in a number of cases the origin of gall-stones to influenza. Since Bernheim in 1880 first drew attention to the connexion between enteric fever and infection of the bile-passages, much attention has been given to the subject. Chiari in 1893 found the *B. typhosus* in the gall-bladder in 19 out of 22 cases of enteric fever, and Hanot and Milian found the organisms in the centre of recently formed gall-stones in 1896. Cushing, Halsted, Richardson, and others have contributed useful facts going to prove the connexion between enteric fever and gall-bladder infection, and between the latter and gall-stones.

Although the causes previously mentioned appear to dispose to gall-stones, there can be no doubt that a bacterial infection of the bile-passages affords the true key to the origin of concretions, both in the gall-bladder and in the bile-ducts.

Symptoms.—In discussing the symptoms of cholelithiasis we must note, in the first place, that gall-stones may be found after death without having produced any symptoms during life. In such cases they are as a rule in the gall-bladder, and not in the ducts; and there are no signs of irritation in the shape of adhesions. But more than this; there can be no doubt that even a large gall-stone may ulcerate its way into

the bowel, and produce symptoms of intestinal obstruction, with few or no signs to indicate that such serious organic mischief has been going on. It follows, therefore, that in considering cases of intestinal obstruction, gall-stones cannot be excluded, though there has been no symptom of cholelithiasis. It is just possible that as some persons may pass urinary stones with few or no symptoms, so others may pass small biliary stones ; this, however, has yet to be proved, and in the meantime it is difficult to explain why in some persons gall-stones should produce such serious trouble and in others none at all. In certain cases there may be a history of dyspepsia, with depression of spirits and a feeling of discomfort or weight, or even ill-defined pains over the right side of the abdomen ; but an entire absence of those characteristic symptoms which give definiteness to diagnosis.

The ordinary symptoms of cholelithiasis are paroxysmal attacks of pain which, occurring at irregular intervals, often without apparent cause, start in the right hypochondrium or in the epigastrium, and radiate thence over the abdomen and through to the right scapula. The attacks are often accompanied by nausea or vomiting and, if severe, by collapse. They may be followed by jaundice with its well-known symptoms, but this is frequently absent. At times a feeling of fulness in the right hypochondrium accompanies the attack ; but the formation of a tumour does not occur as a rule unless the ducts are blocked. Accompanying these special symptoms will usually be found much depression of spirits, want of appetite, dyspepsia, and loss of weight.

According to Naunyn, there is a regular and an irregular form of the disease. The former occurs where the calculi are simply lodged in the gall-bladder, or the stones pass along the ducts ; the latter is seen when there is infectious angiocholitis, with abscess in the liver, fistula, and other complications (see sections on Inflammatory Affections of the Gall-bladder and Bile-ducts).

The following symptoms will be considered in detail :—

(a) *Paroxysmal Pain*.—For the most part the patient complains of pain under the right costal margin or in the epigastrium, whence the pain radiates over the abdomen and to the right scapula ; but in some cases the pain radiates to the left shoulder. These attacks come on suddenly, when the patient is apparently quite well ; and usually end by causing nausea or an attack of vomiting. The vomiting leads to relaxation of the duct, and if the gall-stone be small it may pass on and thus end the attack. The seizures come on without apparent cause, although at times they may appear to be caused by exertion or by taking food. Not infrequently, after an attack has passed off, a dull aching is felt for some time, perhaps until another seizure. Besides the painful attacks which come on at irregular intervals, there is often a persistent dull ache beneath the right costal margin associated with rigidity of the upper part of the right rectus, and the presence of a tender spot midway between the 9th costal cartilage and the umbilicus.

(b) *Vomiting*.—Though as a rule the vomiting is paroxysmal, it may

be almost continuous, and so of itself prove dangerous. In one case of this kind, on which I operated at Sunderland, the patient was so weak from persistent vomiting that I feared she could scarcely bear the operation I had gone to perform ; and even after the cause of irritation had been removed, the vomiting persisted for days : ultimately, however, she made a satisfactory recovery. In another case which I saw in the south of Ireland the vomiting had been so incessant that the patient had been fed almost solely by nutrient enemas for six weeks before I operated ; and even afterwards, though the operation was satisfactory and the after-progress all that could be desired in other respects, the emesis persisted for a fortnight, and ultimately proved fatal from sheer exhaustion. The vomiting as a rule occurs towards the end of a seizure, and in fact frequently determines its cessation. In such cases the stomach contents are first rejected, after which, if the common duct be free, bile is vomited ; at times I have even seen the severe vomiting become stercoreaceous.

(c) *Collapse*.—On several occasions I have seen patients so profoundly collapsed by attacks of cholelithiasis as to lead to a difficulty in diagnosis, the case being more like one of perforation of some abdominal viscus or some intra-abdominal haemorrhage ; but the history of previous seizures, and of the onset of the present attack, will usually help us to arrive at a correct diagnosis. The acute agonising pain may of itself cause death, as in the case of a lady whom I saw in consultation, when gall-stones were diagnosed. The next attack of pain unfortunately proved fatal, and at the autopsy a gall-stone was found half extruded into the duodenum. Sir Clifford Allbutt refers to a case in which death appeared to be solely due to pain, in his article in Vol. III. p. 394. Not only may the agonising pain of a single attack prove fatal, but repeated attacks of pain occurring one after the other, without sufficient interval for recovery, may produce very serious illness, or even death by exhaustion.

(d) *The formation of a tumour* in the region of the gall-bladder is seldom seen in acute cases ; yet it may be noticed with each attack, and it is then due to the violent contraction of the muscular walls of the gall-bladder on its contents. It is, however, a frequent sign in the more chronic cases, as is fully discussed in the section on Tumours of the Gall-bladder. An elongated right lobe of the liver is frequently associated with cholelithiasis, and may give rise to a suspicion of tumour (*vide* p. 11).

(e) The presence of *gall-stones in the motions* after an attack is valuable evidence, but their absence does not negative cholelithiasis. I have operated on many cases and found gall-stones where none had at any time been detected in the motions, although diligently sought for.

The way to search for gall-stones is to let the patient pass the motion into a solution of carbolic acid, to have it well stirred, and then to pass it through a fine sieve with about $\frac{1}{16}$ -inch mesh.

(f) *Jaundice*.—So long as the gall-stones are in the gall-bladder or cystic duct there is nothing to prevent the bile from passing down the common duct into the intestine ; but should the gall-stones be impacted in the common duct, the passage of the bile is obstructed, and jaundice

ensues. Intermittent jaundice may also occur if a small gall-stone in the common duct act as a ball-valve (Fenger).

In these cases a decision concerning operation is difficult; chronic jaundice too often indicates malignant disease, and not only do patients with cancer bear operations badly, but when jaundice is associated with it there is the same tendency to persistent oozing of blood from the wound after operation as there is to spontaneous haemorrhage where no operative measures have been undertaken.

Jaundice may be entirely absent, even in the presence of gall-stones in the common duct; this I have seen on several occasions when the gall-stone was floating, but never when it was impacted in the duct. A slight degree of jaundice often occurs after a gall-stone attack when the concretion is in the gall-bladder or cystic duct; this is due to associated catarrh of the bile-passages or to pancreatic catarrh.

(g) *Ague-like Attacks.*—Ord drew attention to the production of intermittent pyrexia by gall-stones, and stated that his attention had been first called to this symptom by some remarks of the late Dr. Murchison on a case of a distinguished medical officer who, after his return to England, was attacked at regular weekly intervals with paroxysms of shivering, followed by fever and sweating. He was supposed at first to have a recurrence of an old intermittent fever, and later to have hepatic abscess; but at last his symptoms indicated and the necropsy proved that his actual and only disease was a gall-stone so impacted as to produce great irritation, but not complete obstruction of the common duct. Similar cases have been noticed by Charcot, who argued that the fever is due to the absorption of some poison into the blood. Murchison was of opinion that such attacks are not of a poisonous or infective origin, but are due to nervous irritation. From the many cases I have seen I think that both explanations are admissible; the fever being not unlike that known as urethral, in which the same contention as to causation arises, but I am firmly convinced that infection is as a rule the cause of the fever and of the ague-like attacks. In a very interesting and important paper, Professor Osler says that the combination of the following symptoms is characteristic of the existence of gall-stones in the common duct, and is, therefore, valuable in distinguishing between that form of obstruction and malignant tumour: (1) Jaundice of varying intensity, deepening after each paroxysm, which may persist for months or even years. (2) Ague-like paroxysms characterised by chill, sweating, and fever, after which the jaundice usually becomes more intense. (3) At the time of the paroxysm, pains in the region of the liver, with epigastric disturbance. This is fully borne out by my experience, and in many cases of jaundice of several months' duration, in which there was this combination of symptoms, I have removed gall-stones from the common duct by choledochotomy (24).

In addition to the symptoms already mentioned, the following complications may be met with, and may constitute the prominent changes threatening life and requiring treatment; the original cause having perhaps

disappeared, or being masked by more serious sequels :—(i.) Ileus, due to atony of the bowel, leading to enormous distension and to the symptoms and appearance of acute intestinal obstruction, apparently the consequence of the violent pain. (ii.) Acute intestinal obstruction dependent on : (a) paralysis of gut due to local peritonitis in the neighbourhood of the gall-bladder; (b) volvulus of the small intestine; (c) impaction of a large gall-stone in some part of the intestine after ulcerating its way from the bile-channels into the bowel; (d) stricture of intestine or adventitious band originally produced by gall-stones. (iii.) General haemorrhages, the result of long-continued jaundice, either dependent on gall-stones alone or on cholelithiasis associated with malignant disease. (iv.) Localised peritonitis producing adhesions, which may then become a source of trouble and pain, even after the gall-stones have been got rid of. I believe that nearly every serious attack of biliary colic is accompanied by adhesive peritonitis, as my experience is that adhesions are found in all cases in which there have been characteristic seizures. (v.) Dilatation of the stomach dependent on adhesions around the pylorus. (vi.) Ulceration of the bile-passages establishing a fistula between them and the intestine. (vii.) Stricture of the cystic or common bile duct. (viii.) Abscess of the liver. (ix.) Localised peritoneal abscess. (x.) Abscess in the abdominal walls. (xi.) Fistula at the umbilicus or elsewhere on the surface of the abdomen, discharging mucus, mucopus, or bile. (xii.) Empyema of the gall-bladder. (xiii.) Suppurative cholangitis. (xiv.) Septicaemia or pyaemia. (xv.) Phlegmonous cholecystitis. (xvi.) Gangrene of the gall-bladder. (xvii.) Perforative peritonitis due to ulceration or to rupture of the gall-bladder or ducts. (xviii.) Extravasation of bile into the general peritoneal cavity. (xix.) Pyelitis of the right side. (xx.) Cancer of the gall-bladder or of the ducts. (xxi.) Subphrenic abscess. (xxii.) Empyema of the right pleura. (xxiii.) Pneumonia of the lower lobe on the right side. (xxiv.) Chronic invalidism and inability to perform any of the ordinary business or social duties of life. (xxv.) Acute, subacute, or chronic pancreatitis.

Diagnosis.—In the sections on Tumours of the Gall-bladder and on Inflammatory Affections of the Bile-Passages the diagnosis of the complications of gall-stones is more fully dwelt upon ; so that in this section it is only necessary to remark on the diagnosis of uncomplicated gall-stone attacks : under this heading we have to consider the several ailments which may produce painful seizures on the right side of the abdomen. These are :—(α) Hysteria or nervous spasms ; (β) Acute dyspepsia with flatulency ; (γ) Appendicular colic ; (δ) Right renal colic ; (ε) Spinal neuralgia ; (ζ) Malignant growth in or near the liver ; (η) Pyloric stenosis ; (θ) Lead colic ; (ι) Chronic pancreatitis ; (κ) Duodenal ulcer ; (λ) Angina pectoris ; (μ) Tabetic crises.

The diagnosis chiefly rests on paroxysmal attacks of pain, starting in the right hypochondrium, and radiating thence over the abdomen and through to the right scapula—the attacks being often accompanied by vomiting or collapse, and sometimes followed by jaundice, although jaundice is frequently absent. If jaundice be persistent, the presence

of malignant disease may be suspected. If, however, the jaundice be dependent on gall-stones, ague-like attacks will probably be present.

Just as in appendicitis there is tenderness over M'Burney's point, so in gall-stones, with very few exceptions, marked tenderness will be found on pressing the finger deeply over the region of the gall-bladder, or over some point between the ninth costal cartilage and the umbilicus, usually at a point one inch above and a little to the right of the umbilicus.

In several cases that I have seen, the pain in the so-called spasms has been referred to the left side, thence radiating to the left infrascapular region; and in operating on such cases I have found the pylorus adherent to the gall-bladder or cystic duct. In hysteria, the irregularity of the attacks, their association with other neurotic phenomena such as polyuria, globus hystericus, and so forth, together with the absence of collapse and of the physical signs of gall-stones, will enable us to arrive at a correct conclusion. In acute dyspepsia with flatulency, the relief following on simple treatment, the pain over the stomach rather than over the gall-bladder, the discovery of a manifest cause and the absence of serious symptoms distinguish so-called stomach "spasms" from gall-stone attacks. In appendicular colic, the almost universal signs of tenderness at a point midway between the anterior superior spine of the ilium and the umbilicus (M'Burney's point), the presence of a swelling in the right iliac fossa or near it, and the absence of right scapular pain, render the diagnosis of this condition free from serious difficulty, though in cases of phlegmonous cholecystitis with peritonitis the latter has sometimes been attributed to appendicitis instead of its real cause. In right renal colic, the associated urinary symptoms, together with the character of the urine and the pain passing down the right genito-crural nerve into the testicle, are distinctive. In lead colic, the more or less persistent "stomach ache," the absence of the usual gall-bladder paroxysms, and the presence of a blue line on the gums, will usually assist in the diagnosis; but if in doubt, the result of treatment by iodide of potassium and saline aperients will shortly clear it up. In pyloric stenosis, if accompanied by adhesions around the pylorus, the symptoms are not unlike those of gall-stones, with which, in fact, the affection may be associated, as in several cases I related before the Clinical Society in 1893. The presence of dilated stomach, the characteristic vomit, the visible peristalsis of the stomach wall, the pain in the left side of the abdomen, and the absence of the characteristic gall-bladder pain, will usually establish the diagnosis.

In spinal neuralgia, the presence of tenderness over the spine, the course of the pain along the branches of the corresponding spinal nerves, the presence of tenderness of the skin, and the absence of collapse and of vomiting put aside all difficulty.

In malignant disease, the absence of pain and tenderness, or, if pain be present, its continued character, the gradual and persistent loss of flesh, and the more marked failure of strength, usually indicate the serious nature of the affection. The persistence of jaundice when once it super-

venes, the absence of ague-like attacks, and, if the disease involve the head of the pancreas, the almost constant presence of a tumour due to enlargement of the gall-bladder, afford landmarks which as a rule prove true guides ; but in many cases gall-stones exist along with malignant disease, and then these symptoms become indeterminate, though the rapid wasting and loss of strength will often lead to a successful diagnosis of the co-existence of the two conditions. If nodules form in the liver, and if ascites with oedema of the feet supervene, the condition becomes manifest at once.

In interstitial pancreatitis, the symptoms may resemble cancer of the head of the pancreas, from which it may usually be distinguished by a careful examination of the urine and faeces as well as by the beneficial results which follow drainage of the bile-ducts, either by cholecystotomy or cholecystenterostomy. I described a series of such cases first at the Polyclinic (21), afterwards in my Hunterian Lectures on the Pancreas (23), and later in my work on the Pancreas (26). From duodenal ulcer the diagnosis should not be difficult if it be borne in mind that the pain in ulcer tends to come on 2 to 4 hours after meals, and is relieved by food. That the attacks recur daily for several days at the same hours. For other points in diagnosis see my Lecture on Duodenal Ulcer (25).

The so-called diagnostic operations of sounding for gall-stones, and aspiration of a distended gall-bladder, I believe to be futile and dangerous ; a small exploratory incision is far better, whether for information or treatment.

The treatment of gall-stones may be considered under the headings —Preventive, Palliative, and Radical. The two former resolve themselves into medical, the latter into surgical treatment.

Medical Treatment.—The preventive treatment of cholelithiasis is chiefly a matter of diet, exercise, and general hygienic surroundings. As women suffer from gall-stones much more frequently than men, it has been thought that their mode of dress, and especially the wearing of stays, may be one of the causes ; but probably the want of sufficient exercise, with constipation and rich living, its frequent concomitants, are more to blame. In prescribing prophylactic measures one would recommend rational clothing (which of course includes the avoidance of tight lacing), temperance in diet, warm baths, fresh air, and regular exercise. In regard to diet, more depends on temperance than on the choice or refusal of certain foods. In giving directions on diet patients may with advantage be told to avoid over-indulgence in sweet and starchy foods and in rich dishes, which tend to induce dyspepsia. Alcohol should only be taken in moderation, well diluted, and with food.

According to the views expressed in considering the cause of the formation of gall-stones, either a sufficiency of albuminous food in the shape of meats or game should be taken, or farinaceous foods which contain a fair proportion of nitrogen. If there be any benefit in the administration of olive oil, the use of butter or of animal fats, if taken in quantities short of producing dyspepsia, should have a similar effect.

Sir Lauder Brunton gives some valuable hints on treatment, and shews how the system of dieting adopted at certain watering-places, when combined with exercise and the administration of diluent beverages (water being the essential element), has very beneficial results. I have been accustomed for some years to recommend patients suffering from cholelithiasis to drink a tumblerful of the natural Carlsbad water with a little hot water before breakfast, and a tumblerful of simple hot water before the later meals; for I think there can be no doubt that, as a rule, too little water is taken, and the inspissated or stagnant bile and mucous deposit, if not removed, will tend in the long-run to form concretions; just as drains, if not flushed from time to time, will become blocked by the deposit of solid matter. Alkaline saline waters (particularly the hot Carlsbad) act beneficially by stimulating the peristalsis of the digestive tract, and increasing the flow of blood to the abdominal organs. In the peristalsis the bile-passages participate, and the movements of the bowels act as a form of massage, while the diseased mucous membrane benefits by the increased flow of blood. The injection into the rectum of large quantities of hot water serves the same purpose. When gall-stones have once formed, no medicine, so far as we know, can dissolve them or produce any material benefit except by way of palliation; and although numerous remedies have been vaunted as beneficial in the dissolution of gall-stones, their advocates have argued as if the gall-stones were in a test-tube; forgetting, apparently, that no drug can reach the concretions save by a circuitous route, and in an extremely diluted form: thus benzoic acid, benzoate of sodium, salicylic acid, turpentine, ether, chloroform, and numerous other agents reputed to be beneficial, can really have no material effect. I would not for a moment say, however, that rational medical treatment may not restrict the increase of gall-stones already formed, or prevent the formation of new ones, and thus prove really curative, if the patient have the good fortune to part with those already formed.

The experiments of Dr. Brockbank effectually dispose of the supposition that the so-called saline cholagogues have any solvent action on gall-stones; for after allowing concretions to stand in a 1 per cent solution of the various salts for fourteen days and then weighing them, he found that there had been no loss of weight. Among the drugs experimented on were the salicylate, the sulphate, the benzoate, the phosphate, the bicarbonate, and the chloride of sodium; the sulphate of potassium, and the chloride of ammonium. Similar experiments with olive oil, oleic acid, and a solution of *sapo animalis*, yielded far different results. A gall-stone, placed in pure olive oil, in two days lost 68 per cent of its original weight, and then broke up into small pieces. With pure oleic acid a similar result followed in a much shorter space of time: a small gall-stone disappeared in twenty-four hours, and a larger one, after losing 63 per cent of its weight in two days, broke up into small fragments in four days. The effect of a solution of animal soap on the concretions is remarkable: after standing for a few hours in a 5 per cent solution, a gall-stone becomes coated with a bluish-white

filmy material, and in time the solid matter becomes viscid. Since the administration of olive oil is said to exert a curative effect in cholelithiasis, these experiments are interesting: but as there is not the slightest evidence that the oil can reach the gall-stone in the gall-bladder or cystic duct, there must be some other than direct solvent action to explain the beneficial effect; indeed, the effect itself is doubted by some observers, and requires more direct proof before it can be accepted. An explanation is offered in Dr. Brockbank's paper:—"Another explanation of the reported disappearance of the gall-stones after large doses of oil may be derived from the action of soap and fats on cholesterin. A digested fat passes into the circulation from the alimentary canal in three forms—as unchanged fat, and as the corresponding fatty acid and soap. All occur normally in the bile, and the amount present in the bile increases with the amount of fat taken in the diet. Oil, fatty acids, and soaps all dissolve cholesterin readily and break up a gall-stone. If, then, the oil, fatty acid, and soap appear in the bile in increased amount after large doses of oil, it is very probable that the gall-stone is attacked by them, especially by the soap, and in time is dissolved, or so reduced in bulk as to be enabled to pass out into the duodenum." I have tried olive oil in large doses in several cases, and cannot say that I have seen any good to result from its employment, unless it were in one case of impacted calculi in the common duct, on which I operated after the olive-oil treatment had been tried for some weeks; I then found that the gall-stones yielded more readily than usual to the pressure of the finger and thumb, as if the treatment had lessened their consistency. The oil may be administered either by the mouth or by the rectum; in either case from two to ten ounces should be given daily. It is not readily taken except with food, and then it is apt to excite dyspepsia. Dr. Goodhart gives an account of five cases of probable cholelithiasis in which olive oil had been administered with apparent benefit. He remarks: "With reference to the results, I wish to say that it is obvious that I cannot claim for these cases anything more than a suspicion in favour of the value of the administration of oil. In no one of the cases have gall-stones been proved to have passed, and in none of the cases has the improvement been so immediate that effect and cause certainly go together." Kishkin's experiments apparently shew how a mistaken idea of its benefit has arisen. The supposed calculi which were parted with were found to consist of oleic, palmitic, and margaric acids combined with lime; and similar concretions could be produced at any time by giving olive oil to any person suffering from scanty biliary secretion; no true gall-stones were ever found in the motions after the olive-oil treatment.

Belladonna has been said to have a specific action in cholelithiasis; and I can conceive that if a small concretion were passing along the ducts it might, by its special action on involuntary muscular fibre, aid in its expulsion. But my own experience would lead me to disagree entirely with a medical writer who says that a pill containing a quarter of a grain

of belladonna and a quarter of a grain of podophyllin resin is a remedy as nearly approaching a specific as it is possible to obtain.

Massage found a strong advocate in the late Dr. George Harley, who said : "For without doubt, perseverance and opportunity will in the end enable them (the operators) to discover gall-bladders equally as readily as the trained fingers of the expert do, and that, too, even through abdominal parietes so thick that untrained hands cannot so much as make out the boundary of the solid liver through them. While, again, they will ultimately find that they will be able to extrude small impacted biliary concretions, be they in the shape of sand, gravel, or stones, from the bile-duct into the duodenum with as much safety and certainty as they can pass a catheter through a stricture into a human urinary bladder. At the same time, for the sake of the patient's welfare as well as their own reputation, they must never forget to be as careful in the mode of operative procedure in the one case as in the other, as neither operation is invariably unattended with danger. This is especially the case when the manipulative operation has been, unfortunately, delayed until the gall-stones have grown large and hard, and, on account of the prolonged pressure, begun to ulcerate through the tissues they have long pressed against."

It is scarcely necessary to do more than draw attention to the description of the gall-stones at the beginning of this article in order to point out how futile, nay more, how injurious massage must be in many cases, however skilfully performed ; for not only is it unlikely, but in by far the greater number of cases it is utterly impossible that the concretions can be forced through passages as narrow as we know the cystic and common ducts to be. Some time ago I was called to a distance to operate on a patient who had been under this treatment systematically carried out, and had nearly died under the process ; so that I had to operate in a much more unfavourable condition than would otherwise have been the case. Fortunately, however, I was able to remove the gall-stones, and the patient is now well. I can only say that were I the subject of cholelithiasis I would not submit to massage, nor could I conscientiously recommend it ; although it may possibly aid in the expulsion of small calculi, it is impossible to diagnose the absence of large ones, or to know the exact condition of the ducts which may possibly be ruptured by manipulation.

During a gall-stone attack, relief is urgently demanded ; at times the drinking of a pint of water as hot as it can be taken, especially if combined with the application of hot fomentations over the region of the liver, will assuage the pain ; at other times the administration of thirty drops of spiritus etheris in two teaspoonfuls of chloroform water every quarter of an hour will answer the same purpose. In some cases I have found exalgin, in one-grain doses, dissolved in a teaspoonful of hot water and repeated every half-hour for three or four doses, or aspirin in five to ten gr. doses, to prove of service. In many cases, however, the only satisfactory remedy is a morphine injection.

Surgical Treatment.—After medical treatment has been fairly and fully tried and failed, I think both physicians and surgeons are now agreed that surgical measures should be resorted to. Whilst cholecystotomy is generally recognised as the operation to be aimed at in the treatment of affections of the gall-bladder or bile-ducts, especially in cholelithiasis, it is often impossible to say what operation will have to be done until the abdomen is opened.

The indications for operating would seem to me to be as follows:—

1. In frequently recurring biliary colic without jaundice, with or without enlargement of the gall-bladder. (2) In enlargement of the gall-bladder without jaundice, even if unaccompanied by great pain.
- (3) In persistent jaundice ushered in by pain, and where recurring pains, with or without ague-like paroxysms, render it probable that the cause is gall-stones in the common duct. (4) In simple empyema of the gall-bladder. (5) In peritonitis starting in the right hypochondrium. (6) In abscesses around the gall-bladder or bile-ducts, whether in the liver, under or over it. (7) In some cases in which, although the gall-stones may have passed, adhesions remain and prove a source of pain and illness.
- (8) In fistula, mucous, muco-purulent, or biliary. (9) In certain cases of jaundice, with distended gall-bladder dependent on some obstruction in the common duct. In such cases the increased risk must be borne in mind, as malignant disease may be the cause of the obstruction, and operation in such cases is attended with greater danger than ordinary.
- (10) In phlegmonous cholecystitis and in gangrene of the gall-bladder.
- (11) In continuous jaundice due to interstitial pancreatitis, which in many cases is dependent on gall-stones either present or passed, and which without operation may end fatally like cancer of the head of the pancreas, but which is curable by a well-performed cholecystenterostomy.
- (12) In simple tumour of the gall-bladder. (13) In cancer, if the disease is localised.

Supposing the case to be a suitable one for cholecystotomy, and the gall-bladder and ducts can be cleared without great difficulty by means of forceps within and the finger outside the ducts, the opening in the gall-bladder can be sutured to the aponeurosis—which is preferable to skin fixation—and so drained; this I infinitely prefer to immediate suture of the opening. But if the ducts cannot be cleared—now a very exceptional condition—what may be done?

(a) Cholelithotripsy, or crushing of the gall-stones in place by means of the finger and thumb, or by padded forceps. I have in the past successfully performed this operation on many occasions, but have now entirely discarded it, as it is uncertain in its results and apt to be followed by relapse.

(b) Choledochotomy, or incising the duct, whether cystic or common, the incision being afterwards sutured; this is rendered much easier by the operation I suggested (22), which I have found in an experience of 200 cases of choledochotomy to be reliable in practice. The chief points are an extension of the incision upwards, into the space between the

right costal arch and the ensiform cartilage, rotation forward of the liver and a projection forward of the parts to be operated on by means of a sand-bag under the back, or by a specially devised table that will throw the dorsal spine forward (24).

(c) Cholecystenterostomy, or the making of an anastomosis between the gall-bladder and intestine, is easily effected if the gall-bladder be dilated, but with difficulty if the gall-bladder be contracted, as often is the case. I have performed this operation many times, but do not recommend it for gall-stones; reserving it only for such cases of obstruction in the common duct as cannot be removed by operation — for instance, interstitial pancreatitis compressing the bile-duct.

(d) The daily injection of fluids, after an interval of some days, through the cholecystotomy opening, which will either soften or dissolve the concretions. For this, hot water, ether, and ether and turpentine have been used with more or less success; but I think Dr. Brockbank's suggestion to use an injection of olive oil, or of oleic acid, or a 0·5 per cent solution of *sapo animalis*, is worth a fuller trial. After the modern operation in which the ducts can be cleared with almost absolute certainty, this method can seldom be necessary.

(e) Cholecystectomy, or excision of the gall-bladder, can seldom be advisable or necessary as a primary operation in gall-stones where the gall-bladder is not seriously damaged, and where the cystic duct is not ulcerated or strictured, and it is contra-indicated in all cases where the surgeon cannot be certain that the deeper bile-passages are free from obstruction, unless at the same time the cystic or common duct can be short-circuited into the intestine. It may be required as a secondary operation in cases of stricture of the cystic duct, the common duct being free, and is frequently required in phlegmonous cholecystitis, and in contracted and useless gall-bladders. Cholecystectomy is advisable in localised cancer of the gall-bladder and for other tumours.

In cholecystotomy, where it is impossible to bring the margins of the incised gall-bladder into the wound, and where the parietal peritoneum cannot be tucked down to meet the edges of the opening, I have made a tube of the omentum; but in such cases no hesitation need be felt in trusting to a drainage-tube, if the opening in the gall-bladder be sutured firmly around a thick-walled tube, either by several sutures, or by a purse-string suture, and if the tube be fixed in the gall-bladder by an eight-day catgut stitch so as to prevent it slipping out prematurely.

Suture of peritoneum, aponeurosis, and skin by separate stitches effectually guards against ventral hernia, if the patient be kept recumbent for two weeks at least, preferably for twenty-one days, and if a firm oval pad be worn under a belt for a few months subsequently. In all cases strict aseptic precautions should be observed, and the abdomen must be left as clean and dry as possible.

In conclusion, I would emphasise that with due skill and adequate care, operations on the gall-bladder and bile-ducts are among the most successful of the major operations; but as many of them are extremely

difficult, and as it is impossible to say beforehand whether any case may not prove so, I think such surgical work should be undertaken only by those who have had experience in abdominal surgery, and who have witnessed or helped in several operations of this kind. As soon as this rule is understood we shall cease to witness the varying rates of mortality in the hands of different operators—from 50 to almost 0 per cent—and we shall probably find that, excluding cases of malignant disease associated with jaundice, the all-round mortality will not exceed 5 per cent, and the mortality in simple cases will not be 1 per cent. I hope the time is not far distant when it will be fully recognised that though cholelithiasis, so far as its causes and its early treatment are concerned, is distinctly a condition for medical treatment, it is both unjust to the patient and unfair to the profession to continue medical treatment and to postpone surgical aid until serious complications supervene, or the patient is almost, if not quite, past relief.

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DISEASES OF THE PANCREAS

CONGENITAL ANOMALIES.

HAEMORRHAGE.

ACUTE INFLAMMATION AND NECROSIS.

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FAT-NECROSIS.

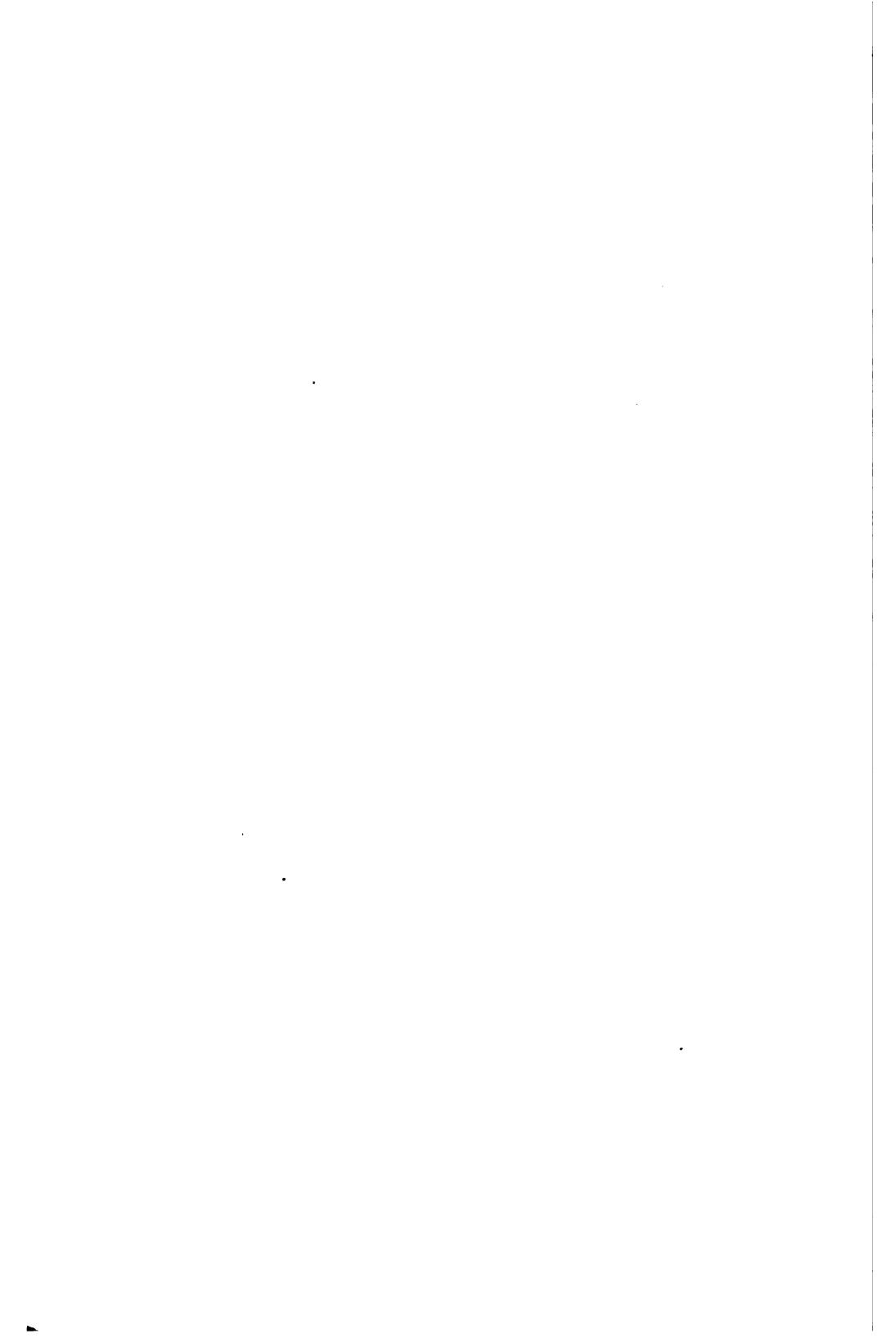
TUMOURS.

CYSTS.

CALCULI.

TUBERCULOSIS.

SYPHILIS.



DISEASES OF THE PANCREAS

By W. CECIL BOSANQUET, M.D., F.R.C.P., and G. NEWTON PITT, M.D., F.R.C.P.

CONGENITAL ANOMALIES ; HAEMORRHAGE ; ACUTE INFLAMMATION AND NECROSIS ; CHRONIC INFLAMMATION AND FIBROSIS ; AFFECTIONS OF THE ISLANDS OF LANGERHANS ; ATROPHY AND DEGENERATIVE CHANGES ; FAT-NECROSIS.

By W. CECIL BOSANQUET, M.D., F.R.C.P.

ACCURATE knowledge of the diseases which affect the pancreas can scarcely even now be said to exist ; such as we possess is almost entirely the product of the investigations since 1888. References to disorders of this organ may, indeed, be found in comparatively ancient literature ; thus Alberti (1578) and Heurnius (1599) wrote of diseases of the pancreas along with those of the mesentery, and suppuration of the gland was known to Tulpus (1641), but no connexion between clinical symptoms and pancreatic disease was established. The earliest observer who drew attention to the coexistence of pancreatic disease and diabetes was Cowley (1788). The work of Fitz (1889), coinciding as it did with the classical experiments of v. Mering and Minkowski, may, perhaps, be looked upon as the starting-point of recent advances ; whilst in the last few years the researches of Flexner and of Opie in America have done for our theoretical knowledge what the surgical skill of Mr. Mayo Robson, following in the footsteps of Senn, Körte, and others, has accomplished on the side of practical treatment.

CONGENITAL ANOMALIES.—An accessory pancreas is occasionally present, and may lie either in the immediate neighbourhood of the pancreas proper or at a distant part of the abdomen. Aberrant masses of pancreatic tissue may occur in the walls of the stomach or duodenum, usually in the submucous coat or beneath the peritoneum. Glinski found an accessory pancreas in the muscular coat of the stomach. In the intestine these nodules of glandular tissue may be found on the summits of intestinal diverticula, which appear to be caused by the traction exerted by the rudiments. A condition has been described in which the duodenum is entirely surrounded by a ring of pancreatic tissue, belonging to the head of the gland. Stenosis of the duodenum may result from this abnormality (see Vol. III. p. 565). Anomalies both of excess and

defect in the number of ducts present, are not infrequently encountered, the presence of a third duct being fairly common. Opie finds that the duct of Santorini is functionless in a large proportion of all cases. This condition is of importance in relation to the presence of calculi in the duct of Wirsung; since, if the duct of Santorini is patent, a channel is available for the escape of pancreatic juice into the intestine; whereas, if both ducts are impassable, complete reteention of the secretion is produced. Rarely the pancreas may be displaced from its normal position and become mobile; it has been found among the contents of umbilical and diaphragmatic hernias.

Pancreatic infantilism, due to congenital deficiency of the gland, has been described by Dr. Byrom Bramwell (see "Infantilism," page 490).

HAEMORRHAGE.—The occurrence of sudden profuse haemorrhage in the neighbourhood of the pancreas and into the substance of the gland constitutes a striking clinical and pathological condition, but considerable confusion in nomenclature has arisen from the prevalence of opposing views as to the causation of the bleeding. The question at issue, which cannot even yet be regarded as settled, is as to the relation borne by the haemorrhage to disease of the pancreas itself; one party holding that the haemorrhage is the primary accident, such alterations as may be met with in the gland being caused by the mechanical action of the blood and by the ensuing inflammatory reaction of the tissues, the other that some preceding disease of the pancreas is necessary to determine the escape of blood into and around it. Pathological appearances are quoted in support of both opinions; it is probable, however, that the nature of the pancreatic secretion renders the latter (secondary) variety of haemorrhage more common here than in other parts, the digestive juice, set free by affections of the cells or ducts, itself tending to cause extravasation of blood in any tissues with which it comes into contact. In some cases the bleeding is definitely peripancreatic, the blood escaping from a point outside the gland and infiltrating the neighbouring parts, as in a case recorded by Trollope and Langdon, in which the pancreas was found lying in a cavity containing half a pint of blood, but was itself free from haemorrhage. In the following account, based mainly upon 94 instances collected from recent literature (1897-1907), only those cases are considered in which the effusion of blood formed the most striking feature, generally going beyond the tissue of the pancreas and infiltrating the surrounding parts. Cases in which scattered points of haemorrhage were found only in the organ itself, are classed under the heading of acute pancreatitis (p. 277).

Etiology.—The causes of haemorrhage into other parts are equally effective in the pancreas. Thus, penetrating wounds by sharp instruments or gun-shots may give rise to bleeding; and a blow on the abdomen or a fall from a height may have the same effect. Haemorrhage often occurs after operations on the pancreas or the biliary passages, and may be the cause of a fatal issue. Atheroma of the arteries supplying the gland may result in aneurysm or direct rupture, and thrombosis of

arteries or veins may lead to extravasation. Apart from injury, it is generally difficult in individual cases to ascertain the cause of the bleeding. Malière found in one case embolism of the pancreatico-duodenal artery, and Hlava found thrombosis of some of the small veins. In a case of Mr. Langton's, in which recovery took place after aspiration of 7 pints of bloody fluid, death occurred two years subsequently from intestinal haemorrhage, and cicatricial stricture of the portal vein was found at the necropsy. Foci resembling infarcts have been described in the pancreas by Brentano and Kirsste, and recently in the case of a man of twenty-seven who died of infective endocarditis with infarcts in the spleen I found the pancreas studded with minute blood-cysts. Small haemorrhages may be found in the pancreas after death from heart-failure, and Nobiling has found them in the bodies of still-born infants and of those dead of suffocation. Rozanek believes that pancreatic haemorrhage may bear some relation to the climacteric, and Hochhaus records its occurrence in a woman with metrorrhagia. Peiser associates the affection with parturition and has collected several instances in which this cause may have been at work. Pancreatic haemorrhage has been noted in connexion with poisoning by phosphorus, mercury, oxalic acid, morphine, and tobacco; in one case of malaria (Ross and Daniels), and in haemorrhagic diatheses (scurvy, haemophilia, purpura).

Of those causes of haemorrhage which are peculiar to the pancreas the most important is, perhaps, the presence of gall-stones in the biliary passages. Opie believes that pancreatic haemorrhage is produced in many cases by regurgitation of bile into the pancreatic ducts, such reflux resulting from blockage of the orifice of the common duct at its entrance into the duodenum; the bile-duct and the duct of Wirsung then remain as a continuous channel behind the obstruction, into which the bile can readily pass. Williams and Busch suggest that the passage of gall-stones may dilate the orifice of the duct and thus allow intestinal contents to enter. The ability of bile to cause acute inflammation of the pancreas is supported by experimental results (see below), but this explanation does not seem to apply to the majority of cases of human disease, gall-stones being found in a comparatively small proportion of cases (18 out of the 94 which I have collected or about 20 per cent).

Flexner finds that, whereas the bile-salts act as violent irritants to the pancreas, the colloid substances (mucin) in the bile have a protective action; he suggests that the relative increase in colloids found in retained bile may explain why the pancreas in some cases shews chronic inflammation instead of acute haemorrhagic lesions.

In a certain number of instances profuse haemorrhage accompanies acute and chronic inflammation of the pancreas. The causation is probably not the same in the two classes of cases. In acute pancreatitis it is reasonable to suppose that damage is done to the secreting cells by the irritant at work, and that digestive juice is thus set free within the substance of the gland. In chronic pancreatitis or fibrosis of the gland, on the other hand, it is usual to find a high degree of atheroma

affecting the pancreatic arteries, and (apart from subacute attacks of inflammation) it is to resulting rupture of one of these that haemorrhage is in such cases to be attributed. Hess believes that soap formed by the action of pancreatic juice on fat is the substance which actually causes haemorrhage : Mr. Cammidge attributes it to glycerin : and trypsin itself has always been assigned as the effective agent.

Much experimental work has been done in order to elucidate the mode of production of pancreatic bleeding. Thus, Thiroloix produced haemorrhage by injecting zinc chloride into the duct of Wirsung, and Carnot by injection of dilute hydrochloric acid, of papain, and of the toxins of the *B. diphtheriae*. Charrin and Levaditi produced the same effect with tetanin introduced into the duodenum, an acute duodenitis resulting without symptoms of tetanus ; they suggest overaction of the pancreas to neutralise the poison. Hlava, who succeeded in causing haemorrhage by injections of gastric juice into the ducts, concluded that the natural disease was due to reflux of undiluted gastric juice from the duodenum, and held that gastric hyperacidity was a factor in the causation of the disease. Flexner caused haemorrhagic inflammation by injection of the bile-salts, and Guleke with intestinal contents ; the latter believes that enterokinase entering the ducts causes conversion of protrypsin into trypsin, and that this ferment induces haemorrhage and inflammation. Simple ligature of the ducts does not result in haemorrhage, but Hess caused bleeding by injections of fat, and Guleke similarly with olive oil, after ligature. Lépine and Panum produced arterial haemorrhage by introduction of lycopodium-powder into the pancreatic arteries (embolism), and Bunge by injecting oil and air into them after preliminary ligature.

Bacteriological investigation of cases of pancreatic haemorrhage has revealed the presence of many different microbes. In the greater number of cases the *B. coli communis* was the predominant organism, but Fitz found the *Staphylococcus pyogenes citreus* ; Dieckhoff streptococci and diplococci ; Larkin a bacillus resembling, but not identical with, *B. coli* and one resembling *B. aerogenes capsulatus* ; Hlava *B. coli* along with pneumococci and a liquefying bacillus ; and Ponfick another special organism not otherwise identified. It is very doubtful whether any of these bacteria can be regarded as having caused the haemorrhage : more probably they represent a secondary infection.

Sex and other Factors.—Of my 94 cases 60 were males and 32 females, and in two cases the sex is not stated. Of those whose age is given fourteen were between 20 and 30, twenty-four between 31 and 40, twenty-four between 41 and 50, seventeen between 51 and 60, and eight over 60. The oldest was 77 and the youngest 19 ; M'Phedran has recorded a case in an infant of 9 months. Many of the patients are obese (35 out of 94 cases). Fatty degeneration of the pancreas is common in such persons, and vessels may perhaps rupture from lack of support ; more probably fatty change occurs in the small blood-vessels themselves. Alcoholic habits also seem to be a factor in its production.

The condition is comparatively rare ; Draper found only 10 cases among 4000 necropsies. Microscopical examination of the pancreas, however, reveals small haemorrhages in a considerable number of cases in which no lesion is visible to the naked eye. Thus, among the 100 cases which I have recently examined for the purpose of this article, haemorrhage was found either in the pancreas or in the surrounding fat no less than 23 times ; in 9 of these there was considerable effusion of blood, in the others minute extravasations. Haemorrhages into the islands of Langerhans were found in several other cases (*vide p. 296*).

Morbid Anatomy.—In cases of haemorrhage the pancreas is generally found much enlarged by infiltration of its tissue with blood ; in Dr. Fison's case it weighed 17 ounces. It is firm in consistency and dark-purple in colour. There is usually some blood or blood-stained fluid in the general peritoneal cavity. The root of the mesentery is infiltrated, and blood may pass in any direction behind the peritoneum, most often in front of and around the left kidney. The lesser sac of the peritoneum may be filled with blood-clot or fluid blood, forming a cyst-like tumour. The peritoneal fat is nearly always dotted over with opaque points of fat-necrosis (p. 299). Petechial haemorrhages may be found in the mucous membrane of the stomach or duodenum. In some instances the pancreatic tissue is torn up by the effused blood, and necrotic fragments may be found surrounded by a mass of fresh or altered clot. Suppuration not infrequently follows haemorrhage, giving rise to circumscribed or general peritonitis or to retroperitoneal abscess. Gall-stones or pancreatic calculi may be found in the ducts. Haemorrhagic effusion may coexist elsewhere, as in the pleural cavity or pericardium. Obesity, cirrhosis of the liver, and granular kidneys are frequent concomitant conditions. Bryant found enlargement of the thyroid.

Microscopically the connective tissue of the pancreas is infiltrated with blood-corpuscles, and strands of fibrin may be visible in the clot. The glandular cells are disorganised and stain badly, presenting a hyaline appearance. Signs of inflammation may be seen in the form of aggregations of leucocytes lying between the lobules of the pancreas. The gland may be the seat of old-standing fibrosis.

Moderate haemorrhages may remain localised and give rise to the formation of cysts in the pancreas ; these may be large and readily recognisable, or so minute as to be scarcely visible without the aid of the microscope. Thus, in the case of a man of sixty-six, who died of a fractured skull, I found the connective tissue forming the stroma of the pancreas honeycombed with minute cysts, the largest about 2 mm. in diameter ; these were evidently due to old haemorrhage, their walls being in places lined by a thin layer of clot, and the glandular tissue around shewing here and there haemorrhagic infiltration. Truhart believes that most pancreatic cysts are produced by haemorrhage.

Blood-clot, whether contained in the vessels or diffused, seems peculiarly liable in the pancreas to take on a hyaline character, the homogeneous masses thus formed being at times only with difficulty

recognisable as blood. Pancreatic connective tissue when infiltrated with blood also presents a peculiar hyaline appearance.

In cases of chronic congestion of the pancreas, masses of dark-brown or black pigment may often be seen lying among the pancreatic cells and in the bundles of connective tissue, representing the remains of blood-corpuscles previously extravasated.

Pathology.—The intense pain which accompanies the onset of pancreatic haemorrhage is probably due to pressure on the nerves of the solar plexus, and the collapse is chiefly due to the same cause, the amount of blood effused in these cases being usually too small to explain such severe symptoms. The vomiting is also nervous in origin, and the obstinate constipation which is generally present may be produced by irritation of the nerves supplying the large intestine, as seemed to be the case in Dörfler's patient (p. 281). Enlargement of the head of the pancreas from distension with blood may perhaps cause direct pressure on the duodenum in some instances. Haematemesis and melaena may result from escape of blood into the stomach and duodenum through the duct of Wirsung, but a haemorrhagic tendency undoubtedly exists in pancreatic disease, as shewn by the petechial haemorrhages recorded in some cases and by the liability to ooze of blood after operations in such patients; blood may thus ooze from mucous membranes as in anaemic conditions and be subsequently vomited or passed *per anum*. The etiology of fat-necrosis is discussed elsewhere (p. 300). The cause of death in pancreatic disease has been assigned to the action of trypsin absorbed into the circulation.

Clinical Phenomena.—In a characteristic case the patient, a man of middle age and stout build, who may have suffered from previous abdominal pain or discomfort, is suddenly seized with agonising pain referred to the umbilicus or epigastrium. He rapidly becomes collapsed, with small thready pulse and cold hands and feet; there is often distinct cyanosis of the face and extremities. Vomiting soon ensues, the contents of the stomach being first ejected and then bilious material. The bowels are obstinately confined. In the course of a few hours the abdomen becomes generally distended, but the distension is greatest in the epigastric region, and this area is intensely tender on palpation. Marked muscular resistance may be noted in this part of the belly. As time passes the vomiting may continue, but it does not become faecal in character. Mental anxiety is marked and delirium is occasionally prominent (Bowby, Munster, Shuttleworth). The pain is continuous, but presents paroxysms of more intense suffering. The patient's strength gradually diminishes, and death ensues in three or four days from exhaustion. The temperature is not usually much raised, apart from coexistent pancreatitis: it may be 99° to 100° F., normal or subnormal. In some instances the pain is less severe, and is colicky, with intervals of cessation. It may radiate to the back or to any part of the abdomen or be referred to the lower part of the chest (Fitz). Women compare the pain to labour-pains. There may be no vomiting, but

merely a feeling of intense nausea. The pulse is often surprisingly quiet, not rising beyond 80 or 90 beats in the minute. Diarrhoea is rare; Torpy records a case in which there was constant desire to defecate, without the power to do so. Haematemesis has been met with not infrequently, and haemorrhage from the bowel has been recorded by several writers (Dally, Leonhardt, Morian, Munster, Ross and Daniels). Truhart among 395 collected cases found a record of haematemesis or melaena in 39. The urine frequently contains a trace of albumin, and excess of the indican is common. Sugar is only occasionally met with (12 cases out of 94; Körte found 2 instances among 41 cases): apparently too short a time elapses before death for this symptom to occur (in Hunt's case it appeared after the patient had undergone operation), or the destruction of the pancreas is not sufficiently complete. Acetone and diacetic acid may accompany the sugar (Hochhaus, Bosanquet). The presence of leucine was noticed by Leonhardt. Blood may appear in the urine (Foott), and suppression of urine is recorded by Mr. Bowlby.

If the effused blood be very large in amount, dulness may be discovered on percussing the patient's flanks; in Trollope and Langdon's case a pulsating swelling appeared in the epigastric region, accompanied by a systolic murmur, thus giving rise to a diagnosis of aneurysm. There may be a high degree of leucocytosis, counts of 39,000, of 37,000, of 22,000, and of 20,000 being recorded.

Diagnosis.—Conditions from which pancreatic haemorrhage has to be distinguished are: acute intestinal obstruction, perforated gastric or duodenal ulcer, embolism of the superior mesenteric artery, acute gastritis, gall-stone colic, appendicitis, and poisoning by irritant metals or poisonous food. At the onset of the malady diagnosis from intestinal obstruction is rarely possible, the vomiting, pain, and collapse being identical. After the lapse of some hours the onset of faecal vomiting, on the one hand, or the appearance of a palpable epigastric swelling, on the other, may give indications of the true condition of things. The pulse is usually more affected in intestinal obstruction. In perforation of a viscus in the epigastric region, the initial symptoms are again almost the same; signs of general peritonitis are, however, likely to ensue rapidly, the tenderness of the abdomen being extreme throughout and not localised in the epigastrium, the abdominal walls becoming rigid and immobile, and superficial as well as deep palpation being intensely painful. Embolism of the superior mesenteric artery may give rise to symptoms almost exactly resembling those of pancreatic haemorrhage; bleeding from the intestine is, however, likely to be more marked, and the vomit may become faecal in character. The existence of heart-disease or of some cause of thrombosis such as an infected wound or recent parturition might suggest the probability of this accident; but pancreatic haemorrhage has also been noted in relation to child-birth. This form of embolism, which appears to be rarer than pancreatic disease, should also be treated by laparotomy. In biliary colic, apart from the intense pain, the general symptoms are less alarming, and jaundice is

likely to supervene at an early period. In metallic poisoning purging is usually pronounced, the poison may be detected in the vomit, and the prospect of death or recovery will usually be fairly determined within the first twelve hours. In food-poisoning more than one person is usually affected, diarrhoea is marked, and cramp-like pains in the limbs are frequently encountered. Should sugar appear in the urine, implication of the pancreas is clearly indicated, but unfortunately this sign is extremely uncommon. Sudden severe abdominal pain in a stout person should always suggest pancreatic disease. Haemorrhage into the upper abdomen is not necessarily derived from the pancreas, as apart from rupture of aneurysms of the coeliac vessels blood may escape from other organs; thus in a case recorded by Grassmann severe bleeding occurred from an adenoma of the liver into the lesser sac of the peritoneum (*vide p. 309*).

Prognosis.—That mild degrees of haemorrhage into the pancreas may be recovered from is evident from what has already been said, but no means at present exist for recognising such conditions during life. In the case of severe bleeding death is the almost invariable termination unless surgical measures are adopted. It may take place within a few hours, or even minutes (Zenker), after the onset, or may be delayed for several days. The average duration of life may perhaps be put at four days, but a patient of Munster's lived eleven days, and one of Hochhaus's fifteen days. Many instances of recovery after surgical interference are now on record. Borchardt collected 15 cases of shot-wounds of the pancreas with five recoveries.

Treatment.—Much discussion has taken place as to the propriety of operating upon the subjects of pancreatic haemorrhage, and surgeons of eminence have expressed an opinion adverse to such interference. Nevertheless, in view of the extreme difficulty of making sure of the nature of the lesion, which closely simulates such conditions as acute intestinal obstruction and gastric perforation, in which surgical operation gives the only chance of recovery, it is certain that laparotomy will appear advisable in many cases. But apart from this consideration, statistics are now clearly favourable to operation. In 1901 Opie collected 25 cases in which laparotomy had been performed, with 2 recoveries (cases of Halsted and Hahn). Since then more successful results have been recorded, and of the 94 cases forming the basis of this article (many probably the same as Opie's cases) 55 were operated upon and 14 recovered. The patient's chance of recovery is thus rendered distinctly better by surgical aid, and it is encouraging to note that the proportion of recoveries has distinctly increased in recent years. Hahn recommends that no severe operation be performed, it being sufficient to pack the neighbourhood of the pancreas with gauze and to arrange for the freest possible drainage. This advice is probably good. If the tension within the pancreas itself is apparently so great that necrosis of the gland is likely to result, it should be incised and packed. Trouble may be caused in the after-treatment by the irritant action of the pancreatic juice, and suppura-

tion at the seat of injury is very likely to occur. In view of the liability to continuous bleeding, it is advisable to administer to the patient full doses of calcium chloride before and after the operation, as is done by Mr. Mayo Robson. The gauze used for packing may be soaked in solution of adrenalin. Should operation be refused or regarded as unadvisable, morphine must be administered in full doses to control the pain, and other symptoms treated as they arise. Strychnine or atropine hypodermically, and hot-water bottles to the extremities, will be needed to combat the collapse, and infusion of hot saline solution may be employed if the patient is blanched.

ACUTE INFLAMMATION AND NECROSIS.—Fitz classified acute inflammation of the pancreas under the headings of Haemorrhagic, Suppurative, and Gangrenous Pancreatitis. The difficulty of distinguishing between cases of simple haemorrhage and those due to a preceding inflammation has already been noticed: apart from the instances in which haemorrhage is the prominent feature, there is nothing to be gained by separating cases of acute inflammation in which there is some amount of haemorrhage from those in which this phenomenon is absent. Nor is gangrenous inflammation clearly marked off from the haemorrhagic or from the suppurative forms, both of which frequently lead to necrosis of portions of glandular tissue. It therefore seems most convenient to consider in the present section all cases of acute inflammation of the pancreas, whether they appear as simple phlegmonous inflammation, as suppuration, or as gangrene or necrosis. This last readily ensues in all severe lesions, owing to the action of the pancreatic juice upon the injured tissue.

Necrosis of the pancreas may result, as has already been stated, from haemorrhage into the substance of the gland, owing to actual laceration of its tissue, to the pressure of the effusion when retained within its capsule, or to poisonous products set free in the process. In cases of acute inflammation large portions of the gland may become gangrenous from the direct destructive action of the bacterial toxins; or the nutrition of the pancreas may be impaired by suppuration round it. But in addition to these cases others occur in which areas of necrosed tissue are met with in the pancreas, apart from obvious inflammation. Chiari maintains that a primary self-digestion of the gland may occur, and that this may be the starting-point of other lesions, such as haemorrhage, rather than the result of antecedent affections. It is clear that, as the pancreas does not normally digest itself, some explanation is needed of the cases in which this phenomenon occurs. Embolism and thrombosis of vessels might lead to injury or death of certain lobules, which might then be digested like other dead material; but such occurrences are not often demonstrable. Further, it is now generally believed that the pancreatic juice, as it is secreted, contains only inert protrypsin, which subsequently gives rise to active trypsin by interaction with the ferment of the intestinal juice (enterokinase). Hence some special condition would be necessary to bring about self-digestion of the pancreas.

Pólya has suggested that the cause of pancreatic disease is to be found in the entry of intestinal contents into the duct of Wirsung, whereby the change of protrypsin into trypsin is effected within the pancreas : the cells are thus exposed to the influence of a ferment which they are not normally called upon to resist.

Etiology.—In the pancreas as in other organs pathogenetic bacteria are the main cause of inflammation. Infection may be carried to the pancreas by way either of the ducts or of the blood-vessels and lymphatics, or by direct spread of inflammation from contiguous parts. According to the degree of virulence of the irritant at work there will ensue either an acute inflammation — haemorrhagic, suppurative, or gangrenous—or a chronic fibrosis (chronic interstitial pancreatitis).

Infection by way of the blood-vessels is probably much less common than that through the ducts. Suppuration may be met with in the pancreas in cases of general pyaemia and of infective endocarditis. Suppuration in the area drained by the portal vein is less likely to affect the pancreas than the liver, but abscesses may be met with in both organs simultaneously, a retrograde thrombosis or abnormal currents in the veins being responsible for the pancreatic infection. Direct spread of inflammation may result from a gastric or duodenal ulcer ; whilst in cases of acute peritonitis some degree of superficial inflammation of the pancreas is not uncommon, and more extensive affection may occur, as in a case of appendicitis recorded by Dr. Mahomed.

Much stress has been laid by some writers upon the connexion between gall-stones and acute inflammation of the pancreas. A study of cases recently recorded does not support the view that this affection is the determining factor in the majority of instances, only 19 out of 97 cases which I have collected being connected or coincident with cholelithiasis. In two others calculi were present in the pancreas itself. It is not impossible, however, that gall-stones may have been present, but overlooked, in other instances.

Injury of any kind may lead to suppuration in the pancreas, bacteria readily invading damaged tissue, and haemorrhagic effusions may also suppurate : the possibility of this latter occurrence enhances the difficulty of classifying recorded cases, in many of which the description of the fluid evacuated strongly suggests that the primary occurrence had been haemorrhage. This may, however, have been a secondary condition.

Inflammation of the pancreas may occur in many infective diseases (enteric fever, influenza) ; suppuration of the gland was recorded in a case of small-pox by Blancard in 1688. A specific metastatic inflammation appears to occur in mumps (Jacob, Priestley). Vierordt records a case of necrosis due to the presence of many small ascarides in the ducts, and Drasche one in which an adult ascaris was found in a pancreatic abscess.

Among 105 collected cases of acute pancreatitis Egdahl found that 44 were associated with gall-stones, 32 with gastro-intestinal disturbances, 11 with mumps, 3 with injury, and 2 with previous enteric fever.

Appendicitis and embolism each accounted for 2 cases, and 1 or perhaps 2 cases were due to a pyaemic condition accompanying an outbreak of boils.

The experiments already recorded under the head of Haemorrhage apply with equal or greater force to inflammatory conditions of the pancreas, the haemorrhage being in almost all such instances secondary to inflammation. A large number of different bacteria have been isolated in cases of pancreatic suppuration : thus, to quote recent observers, the *B. coli* was found by Brennecke, Etienne, Opie, and Strübe ; streptococci in the local lesions by Germain and Christian, and in the blood by Brugsch and König ; the pneumo-bacillus by Marwedel. *Proteus vulgaris*, *B. pyocyanus*, *B. lactic aerogenes*, and various unidentified germs have also been found, and even sporozoa have been described in these cases (Devoto). Carnot found that tuberculin, as well as papain and croton oil, when injected into the pancreas, might cause suppuration.

Age and Sex.—As in the case of haemorrhage, males are more often the subjects of acute pancreatitis than females, but the disproportion is not so marked : thus of 97 cases from recent records, embracing simple inflammation, suppuration, and necrosis, 59 were males and 37 females (one not stated). Among 75 cases of suppuration Page found 48 men and 27 women. This group of affections also occurs more often than haemorrhage at comparatively early ages : thus Page found 16 cases below thirty, 30 between thirty and fifty, and 17 over the last age. Among the cases which I have collected 22 were under thirty, 18 between thirty-one and forty, and 50 above this last age ; 7 cases of suppuration occurred in persons between twenty and twenty-five. The youngest case which I have found was ten years old, a boy who had signs of acute pancreatitis as a sequel of mumps ; the oldest seventy-five, a man under the care of Dr. Hogarth and Mr. Moynihan, who died of suppurative pancreatitis ; but there seems ground for questioning whether haemorrhage had not been here the primary occurrence.

The liability of fat persons to suffer from pancreatitis is noticeable, about 25 per cent of the recently recorded cases being of this character. Alcoholic habits have also been shewn to be a disposing cause in about 20 per cent of these cases. A history of past attacks of abdominal pain and vomiting, or of indefinite dyspepsia, is given by many patients.

Morbid Anatomy.—In the mildest cases of acute pancreatitis nothing may appear amiss with the gland when it is removed at necropsy ; in such cases microscopical examination will shew that the septa of connective tissue passing between the lobules are infiltrated with leucocytes, whilst the glandular cells are swollen and granular. Areas of necrosis may be present, and here and there some escape of blood may have occurred. In more acute cases the organ looks pink or reddish, especially when it is seen at an operation during life ; after death the redness subsides to a great extent and the gland looks yellowish with some pinker areas. Patches of dead-white necrotic fat may appear scattered throughout the organ. The pancreas feels firm or even hard to the touch : it has been compared to a pudding tightly tied up in a bag or even to a plaster-

of-Paris cast lying against the vertebrae. If suppuration have occurred the general colour may be greenish-grey or dirty brown: on section there may either be a general infiltration of the gland with pus, which wells up as from a sponge, or there may be a localised abscess, usually in the head of the organ, with ragged necrotic walls. The rest of the gland may be found infiltrated with leucocytes, and haemorrhagic areas are often visible. Calculi may be found in the pancreatic ducts, and a chronic fibrosis may have preceded the final acute inflammation.

In many cases the suppuration is around rather than in the pancreas, the gland lying in a collection of pus and necrotic adipose tissue. Necrosis of some portion of the pancreas is usually present in such instances. The pus may pass into the lesser sac of the peritoneum, in which large amounts may collect. In many of these cases the fluid is described as dark brown or reddish in colour, and may shew yellowish particles floating in it: the colour is suggestive of altered haemoglobin arising from a haemorrhagic effusion which has subsequently suppurated, or from secondary effusion of blood as the result of inflammation. The yellow patches represent necrotic fat. In other instances the pus passes down in front of one or other kidney, according as the head or the tail of the pancreas was the original seat of suppuration: a large bilocular abscess cavity extending down on both sides of the vertebral column was found in Tilden Brown's case. The pus may burrow for a long distance and reach the pelvis, finally escaping by the vagina, as in Guinard's case; or the stomach or bowel may be perforated by the abscess and pus be vomited or passed *per anum*; or a subphrenic abscess may be formed and extension of inflammation to the pleura result. It has been suggested that in many instances of suppuration beneath the diaphragm the pancreas may have been primarily at fault. Pancreatic ferments may be demonstrated in the contents of the abscess, and portions of necrotic fat or of the pancreas itself are often found floating in it. The fluid is sometimes fetid and gas may be liberated by the action of the micro-organism present. Dr. Rolleston found tyrosine in the fluid in one case.

Necrotic portions of the pancreas are usually brownish or blackish in appearance, the colour being often due to haemorrhagic infiltration. In less acute cases they may look grey or yellowish-white, or may only be discovered on microscopical examination. Microscopically, the cells of the acini are swollen and confluent, more or less separated from the stroma, and often lying in a confused mass. Portions shewing the normal acinous arrangement can, however, generally be found. The cells stain badly or scarcely at all, and even the nuclei are hardly distinguishable. The whole area affected may look homogeneous and hyaline, or granular and structureless. Blood is often visible in the mass or remains of haemoglobin in the form of dark brown or blackish granules and lumps. When necrosis of a portion of the pancreas has occurred during life and the patient has survived for some days, inflammatory reaction occurs round the dead part, and leucocytes may be seen collected at its periphery. If this phenomenon is not visible, it is

practically impossible to distinguish true necrosis from post-mortem digestion of the gland. The spleen has been found enlarged in several cases. Acute inflammation of the duodenum may also be met with (Opie, Simon and Stanley); it may either represent the original seat of inflammation, or be secondarily implicated by extension from a suppurating focus in or around the pancreas. Foci of necrosis may be found in the liver, or areas of suppuration due to pylephlebitis. Acute pleurisy or empyema may also be present. Fat-necrosis is demonstrable in a large number of cases.

Pathology.—The symptoms met with in acute pancreatitis can for the most part be readily explained on the same grounds as those in haemorrhagic cases (p. 274). The constipation met with in these cases is usually attributed either to direct pressure of the swollen gland on the duodenum, which is sometimes entirely surrounded by glandular tissue, or to peritonitis affecting the intestines in contact with the infective area. In one case, recorded by Dörfler, a peculiar spasmody contraction of the descending colon was found at the necropsy, the gut above this being dilated: it would seem, therefore, that the condition had occurred during life and was not comparable with agonal intussusceptions; it must then have been due to nervous irritation, which may possibly be the cause of the phenomena of intestinal obstruction in other cases. Jaundice may be produced as in chronic pancreatitis by pressure of a swollen pancreas on the bile-duct; indeed Mr. Mayo Robson and more recently Dr. Phillips have put forward the view that what is called "catarrhal jaundice" is really produced by inflammatory swelling of the pancreas, resulting from catarrh of its ducts. The existence of foci of necrosis in the liver has been explained on the ground of entrance of pancreatic juice into the portal vein, or more recently as due to embolism of living pancreatic cells which continue to secrete trypsin when lodged in the liver. The peculiar latency of the affection in some suppurative cases can be paralleled by similar occurrences in empyema and in other localised suppurative foci: the degree of constitutional disturbance produced depends on the virulence of the organisms and on the facilities for the absorption of the toxins which they produce. The degrees of fever and of leucocytosis in the blood are similarly influenced.

The relation of pancreatic disease to glycosuria is discussed in the article on diabetes mellitus in Vol. III. The rarity of this symptom in acute pancreatitis is probably because, on the one hand, it is unusual for anything approaching total destruction of the gland to occur; whilst, on the other hand, death ensues in many instances within a few days of the onset of the inflammation, thus affording too short a time for this phenomenon to be produced. In experimental diabetes produced by removal of the pancreas in animals, sugar does not appear in the urine for many hours or even some days after the operation. The rapid course of acute pancreatitis also explains the absence (as a rule) of those symptoms of pancreatic insufficiency, such as fatty stools and failure to digest meat-fibre, which are seen in chronic pancreatitis.

A sympathetic connexion between the pancreas and the salivary glands has been supposed to exist, the idea originating as far back as Regnerus de Graaf (1682). Salivation (sialorrhœa) as a sign of pancreatic disease has been described by several writers (Rahn, Franck, Fourcroy, Wickmann), but the phenomenon does not seem to have been recently recorded. Italia states that the salivary glands may be found enlarged if the pancreas is experimentally removed, and that in one case in which the parotid glands were removed the pancreas appeared hypertrophied; a trace of sugar may appear in the urine as a temporary result of this last operation. Truhart records double parotitis in one case of acute pancreatic inflammation, but this must be regarded as pyaemic. Lorand believes that there is an antagonism between the pancreas and the thyroid gland.

Clinical Phenomena.—The onset in the most acute cases may be practically sudden and indistinguishable from that of haemorrhage; but, as a rule, the pain is less agonising at the moment of onset, and may arise gradually, only reaching its maximum intensity after some hours. Nausea or vomiting ensue, and the bowels are constipated. The tongue is furred, the pulse frequent, and fever of varying degree is usually present. The pain is in most instances referred to the epigastrium or to the umbilical region, but it may be localised in other parts, right iliac, splenic, praecordial, or scapular region. Dörfler records an instance in which it was at its maximum in the loins, extending to the thighs and legs so as to resemble sciatica. Pain may be comparatively slight in subacute cases, as in Thayer's patient who complained only of a "sore feeling" in the epigastrium. Fever is very variable. A temperature of 104° F. may be met with, or it may never rise above 99° or 100° F. The frequency of the pulse is equally variable.

Chronic (latent) cases of pancreatic suppuration sometimes occur. Thus, Page records the case of a man of fifty-three, alcoholic, who suffered for fifteen days from headache, malaise, weakness, loss of appetite, and constipation; some jaundice finally appeared and there was slight fever. Pleural friction made its appearance on the twentieth day, but there were no localising signs. Death ensued in about two months with increasing weakness; at the necropsy the pancreas was found riddled with suppurating channels. In a case recorded by Porter rupture of a pancreatic abscess, with resulting general peritonitis, was the first indication of the existence of the affection; death occurred in sixty-six hours.

In severe cases the general condition of the patient rapidly becomes alarming; there are collapse, cyanosis, and great mental anxiety. The skin may be covered with sweat; the breathing is laboured, and death apparently imminent. More often after the acute onset some improvement takes place, and relapse followed by renewed improvement may occur several times. Rigors are not infrequently recorded in suppurative cases. The blood usually shews leucocytosis, counts of 15,000 to 20,000 being common, whilst Woolsey counted 26,000 and Murray 40,000.

This phenomenon is, however, not invariably present. The condition of the urine is not often characteristic, a trace of albumin being the most frequently noted abnormality ; glycosuria is the exception, being found, among the recent cases which I have collected, only by Brentano, Dörfler, Marwedel, Nash, and Woolsey. In Brentano's case, in which the pancreas underwent necrosis, sugar only appeared after the patient had been operated on, and remained present afterwards without symptoms of increased thirst or appetite. In Marwedel's case, on the other hand, the glycosuria disappeared after the operation, and in Nash's case it likewise subsided in the course of six months. Acetone and diacetic acid may be found without sugar (Cammidge). Some degree of jaundice is often present.

Symptoms occasionally met with are diarrhoea, which may ensue after the primary constipation ; and fatty stools, noticed by Brugsch and König, Deaver, and Toye. Undigested muscle-fibres may accompany the fat (Bardenheuer). Pus and blood may be passed *per anum*, and Guinard records passage of pus *per vaginam*. Haematemesis occurred in Dr. Mahomed's case, and in one of Dr. Newton Pitt's pus was vomited. Pigmentation of the abdomen was noted by Fitz and recently by Guinard, but seems to be very rare ; in Guinard's case it disappeared after operation. In Dr. Hogarth and Mr. Moynihan's case blotches (haemorrhagic ?) appeared on the abdomen and subsequently faded away : petechial haemorrhages have several times been observed. A patient of Tomaschny's suffered from repeated convulsions, but this woman was insane. Caven and Oldright, however, also record this symptom, and Guleke noted spasm of the fore-legs in a dog dying of pancreatic necrosis experimentally produced by injection of olive-oil.

Physical examination of patients suffering from acute pancreatitis generally reveals distension of the abdomen, especially in the epigastrium. Peristaltic movements of the intestines are absent. Tenderness is also complained of in the same region, making palpation difficult or impossible. Resistance may be felt in the epigastric or umbilical region, and sometimes a definite tumour may be distinguished : the position, shape, and size of this vary with the exact condition present. In simple acute pancreatitis a sausage-shaped mass may be palpable, lying transversely above the umbilicus, or a local tumour may be palpable, deeply situated in the right hypochondrium. When pus has formed, a larger, less definite mass may be felt in either of the regions just mentioned or in the left hypochondrium ; fluctuation has rarely been recognisable. Dulness in the flanks may exist, if the pus has collected in the general peritoneal cavity. A retracted condition of the abdomen was observed by Milnes. The fluid which escapes after an operation for pancreatic disease, or which is found collected in the neighbourhood of the organ, may contain the three pancreatic ferments, which can be recognised by appropriate tests ; or one or two of them only may be demonstrable.

Diagnosis.—In the most acute cases of pancreatitis diagnosis may be impossible ; but in the presence of a sudden attack of violent pain in the epigastrium, with vomiting, constipation, localised tenderness and

distension, and a proneness to collapse, the possibility of pancreatic affection should always be considered. The points already noted as bearing on the question of pancreatic haemorrhage are equally applicable here (see p. 275). In perforative peritonitis arising from ulcer of the stomach or duodenum, the abdominal distension and tenderness more rapidly become general; collapse is earlier and more marked; vomiting is at first less prominent; the pulse is more frequent; the temperature is usually subnormal at the outset. None of these features is, however, invariable. In less fulminating attacks of pancreatitis there is more time to watch the case and to recognise the true state of affairs. The localised nature of the tenderness and distension becomes apparent, and some improvement is likely to occur. Alternate improvement and retrogression are suggestive phenomena. The occurrence of jaundice without disease of the liver is characteristic of pancreatic affections. Leucocytosis will suggest an inflammatory, probably a suppurative, condition at the seat of trouble, but will not distinguish pancreatic disease from other local lesions in the epigastric region. In chronic cases increasing weakness and emaciation are marked; fatty stools may be met with; and the remittent or intermittent temperature suggests suppuration. If sugar appear in the urine, affection of the pancreas will be rendered almost certain; but unfortunately this sign is exceedingly rare. Mr. Cammidge found acetone and diacetic acid present (without sugar) in the urine of 4 cases out of 7 of pancreatic disease; in 5 cases there were large quantities of calcium oxalate crystals; in 4 bile was present, and in 5 urobilin. Lipase has been found in the urine in experimental pancreatitis, but does not appear to have been looked for in human disease. The blood may be examined for the presence of pathogenetic germs (*streptococci*, etc.).

The present may be a convenient place in which to allude to the test for pancreatic disease suggested by Mr. Cammidge. As the result of extensive researches he found that a peculiar substance, probably pentose, was contained in the urine in those cases, and could be recognised by its formation of crystals (osazone) in the presence of phenyl-hydrazine. His latest method of procedure is as follows:—

"A specimen of the twenty-four hours' urine, or of the mixed morning and evening secretions, is filtered several times through the same filter paper and examined for albumin, sugar, bile, urobilin, and indican. A quantitative estimation of the chlorides, phosphates, and urea is also made, and the centrifugalised deposit from the urine examined microscopically for calcium oxalate crystals. If the urine is found to be free from sugar and albumin, and of an acid reaction, 1 c.cm. of strong hydrochloric acid (specific gravity 1.16) is mixed with 20 c.cm. of the clear filtrate, and the mixture gently boiled on the sand-bath in a small flask having a long-stemmed funnel in the neck to act as a condenser. After ten minutes' boiling the flask is well cooled in a stream of water, and the contents made up to 20 c.cm. with cold distilled water. The excess of acid present is neutralised by slowly adding 4 grams of lead carbonate. After standing for a few minutes to allow of the completion of the reaction, the

flask is again cooled in running water and the contents filtered through a well-moistened, close-grained, filter-paper until a perfectly clear filtrate is secured. The filtrate is then well shaken with 4 grams of powdered tribasic lead acetate and the resulting precipitate removed by filtration, an absolutely clear filtrate being obtained by repeating the filtration several times if necessary. Since the large amount of lead now in solution would interfere with the subsequent steps of the experiment, it is removed either by treatment with a stream of sulphuretted hydrogen or, what I have found to be equally satisfactory and less disagreeable, by precipitating the lead as a sulphate. For this purpose the clear filtrate is well shaken with 2 grams of finely powdered sodium sulphate, the mixture heated to the boiling point, then cooled to as low a temperature as possible in a stream of cold water, and the white precipitate removed by careful filtration; 10 c.c.m. of the perfectly clear transparent filtrate is made up to 18 c.c.m. with distilled water and added to 0·8 gram of phenyl-hydrazine hydrochloride, 2 grams of powdered sodium acetate, and 1 c.c.m. of 50 per cent acetic acid contained in a small flask fitted with a funnel condenser. The mixture is boiled on a sand-bath for ten minutes, and then filtered hot through a filter paper moistened with hot water into a test-tube provided with a 15 c.c.m. mark. Should the filtrate fail to reach the mark, it is made up to 15 c.c.m. with hot distilled water. In well-marked cases of pancreatic inflammation a light yellow, flocculent precipitate should form in a few hours, but it may be necessary to leave the preparation to stand overnight before a deposit occurs. Under the microscope the precipitate is seen to consist of long, light yellow, flexible, hair-like crystals, arranged in sheaves which, when irrigated with 33 per cent sulphuric acid, melt away and disappear in ten to fifteen seconds after the acid first touches them. The precipitate should always be examined microscopically, as it may be difficult to determine the characters of a small deposit with the naked eye, and so cases giving only a slight reaction may be overlooked. To exclude traces of sugar, undetected by the preliminary reduction tests, a control experiment is carried out by treating 20 c.c.m. of the urine in the same way as in the test described excepting for the addition of the hydrochloric acid.

The urine employed for the experiment should be fresh, and not have undergone fermentative changes. If alkaline in reaction it should be made acid with hydrochloric acid before the test is commenced; any glucose that may be present should be removed by fermentation *after* the urine has been boiled with the acid, and the excess neutralised."

For the more complicated method originally suggested by Mr. Cammidge, in which two separate reactions were employed, the urine in the second being first treated with mercuric chloride, reference may be made to the original Arris and Gale Lectures, 1904. The claim, that by a comparison of the results obtained in the two experiments it was possible to distinguish the particular form of affection—*inflammation or tumour*—of which the pancreas was the seat, is difficult to credit, and is now apparently abandoned by its author. In the hands of its inventor the pancreatic reaction has given good results. Other observers have not, however, been able to claim equal success. Criticisms, both practical and theoretical, have been advanced by Drs. Ham and Cleland and by Dr. P. S. Haldane. Further, the test necessitates a somewhat lengthy and compli-

cated procedure, which can only be carried out in a laboratory, so that it is not always available. The administration of calcium salts to the patient interferes with the development of the pancreatic reaction in the urine.

Prognosis.—Owing to the differences in the severity of individual cases it is difficult to formulate any general principles for judging of the probable outcome of the affections included in this group. Simple acute pancreatitis, such as that occasionally seen in mumps, tends to run its course to recovery. Many cases of mild infection undoubtedly resolve without treatment, or lead to chronic induration of the gland. In acute infections the danger arises from suppuration or necrosis of the pancreas. Here the danger is great, but many successful cases of operative interference are now recorded. Some statistics are given in the next paragraph. Cases apparently moribund have been known to recover after operation.

Treatment.—The treatment of simple acute inflammation of the pancreas is expectant, apart from the existence of symptoms pointing to necrosis of the gland. Morphine must be given for the pain, and hot fomentations may be applied to the abdomen. Milk diet is essential; ice may be sucked or sips of hot water given for thirst. The bowels may be opened by enemas if desired. In all grave cases operation is called for, to provide for the escape of pancreatic secretion, pus, or blood. It is well, perhaps, to defer laparotomy as long as can safely be done, as Mikulicz's statistics favour a waiting policy. Thus, of 46 cases of acute pancreatitis in which operation was performed early, only 9 recovered; whereas of 35 cases in which it was deferred, 18 survived. Among the cases which I have collected 38 were operated on for suppurative conditions, with 25 recoveries and 13 deaths; twenty for non-suppurative conditions, with 9 recoveries and 11 deaths; whilst in cases of necrosis of the gland 12 operations are recorded with only 2 recoveries. Little can be learned from these figures, as it is difficult to classify recorded cases into one or other group. In suppurative cases operation is indispensable; I have not found any record of such a case recovering without surgical aid. The high mortality in the case of necrosis is explained by the severity of the condition, which is usually due to a virulent infection.

· **CHRONIC INFLAMMATION (Chronic Interstitial Pancreatitis, Fibrosis of the Pancreas).**—Under this heading it is convenient to include all conditions characterised by an increase of the fibrous stroma of the pancreas, whether they be due to inflammation or to secondary fibrosis consequent upon atrophy of the glandular cells, inasmuch as it is impossible in many cases to decide after death to which of the two processes the fibrosis is attributable.

Etiology.—The causes of fibrosis of the pancreas may be divided into (1) infective, (2) toxic, and (3) degenerative. Possibly to these should be added (4) mechanical—fibrosis resulting from interstitial effusion of blood: the condition met with in cases of old haemorrhage, in which there is formation of small cysts with various degrees of surrounding fibrosis, suggests the possibility of this mode of causation (*vide p. 273*).

(1) No definite line can be drawn between subacute and chronic cases of pancreatitis. An example of a condition lying on the border-line may be seen in a case recorded by Mr. Moynihan, of pancreatitis following enteric fever. Enteric fever is not infrequently recorded in the past history of patients suffering from chronic pancreatitis, and in this case the bacilli were demonstrated. It is noteworthy that the agglutination-reaction with *B. typhosus* is often given by patients suffering from jaundice. Probably the *B. coli* is the most frequent cause of chronic inflammation of the pancreas. This view is supported by the experiments of Carnot, who found that an invasion of the pancreas by this organism occurred as a result of many forms of injury to the gland ; as, for instance, after injections of *B. tuberculosis* or of tuberculin, after operations on the biliary tract, and after injection of croton oil into the duodenum. The direct introduction of virulent cultures of *B. coli* into the duct of Wirsung caused acute haemorrhagic inflammation, less virulent organisms gave rise to suppuration, whilst attenuated strains produced sclerosis of the pancreas. It is not uncommon to find in pancreases, which are apparently quite normal, small collections of round cells lying just outside some of the smaller ducts : these probably represent the effects of irritants (micro-organisms) which have passed out from the ducts into the surrounding tissue of the gland. Such collections of cells represent the starting-points of patches of interstitial fibrosis, which may extend further and involve much of the pancreas, as fresh foci of inflammation arise. Fibrosis of the pancreas is not uncommon in congenital syphilis ; and gummatous infiltration may cause extensive irregular fibrosis in the acquired form of the disease. (See p. 316.)

(2) Among toxic causes of chronic pancreatitis the most important is probably the abuse of alcohol. In the majority of cases of cirrhosis of the liver the pancreas is simultaneously affected : thus, Steinhaus found pancreatic fibrosis in 11 out of 12 cases of cirrhosis, and Klippel and Lefas in every one of 8 cases examined. Of 6 cases of hepatic cirrhosis I found only 1 in which the pancreas was unaffected. The fibrosis in such instances is more extensive than could well be referred solely to backward pressure in the portal vein, and the condition of the pancreas is therefore probably produced in the same way as is the cirrhosis of the liver. The pancreas may also be affected alone in alcoholic subjects. The chronic interstitial pancreatitis found in cases of haemochromatosis is possibly due to the action of the same poison which causes the destruction of blood-corpuscles and the resulting pigmentation.

The relation of pancreatic fibrosis to tuberculosis is at present uncertain. Carnot produced sclerosis of the pancreas by injections of tuberculin and also of tubercle bacilli, and records some cases occurring in comparatively young persons, in which fibrosis of the pancreas coincided with tuberculous disease elsewhere. In one instance the fibrosis was limited to the tail of the gland, which was in contact with a tuberculous kidney. He suggests that tuberculous toxins are eliminated in the pancreatic juice and cause irritation in the process of excretion. The

production of pancreatic fibrosis by tuberculous toxins is supported by Italia. I have met with a case of well-marked interstitial change in the pancreas of a child of 4 years who had died of general tuberculosis; such fibrosis is rare at this age apart from syphilis, of which there was no evidence. In six pancreases, however, taken from patients who had died of pulmonary tuberculosis in the Brompton Hospital, I failed to find any distinguishable sclerosis.

Fibrosis resulting from obstruction of the pancreatic ducts is also probably toxic in origin, and due to the action of the pancreatic juice under pressure. A very large number of experiments have been performed to elucidate the effects of ligaturing the pancreatic ducts, and the great majority of observers have found fibrosis of the gland to ensue. Thiroloix injected the ducts with soot and obtained complete fibrosis of the whole pancreas, and other experimenters have produced the same effect with fat, oil, and similar substances. It must be borne in mind, however, that it is difficult in many such cases to exclude the action of bacteria, and the same is true of cases of natural obstruction in the human subject. Such a condition is brought about by impaction of a gall-stone in the ampulla of Vater, or of pancreatic calculi in the ducts of the gland, or by the pressure upon these of tumours arising either in the gland itself or in the duodenum. Mr. Mayo Robson suggests that it depends on the course of the bile-duct whether chronic pancreatitis results from an impacted gall-stone or not; a stone lodged in a duct which passes through the pancreas gives rise to this affection, whereas if the duct be entirely outside the gland no such disease ensues.

(3) Fibrosis of the pancreas as a degenerative change is common; a large proportion of all persons dying at ages over 40 exhibit some sclerosis of the pancreas. Thus, in 100 unselected cases dying from all causes examined previously to 1905 I found 15 instances of more or less marked fibrosis: 54 of these patients were over 40, and of these 10 were affected with sclerosis. Among 100 unselected cases examined in the last two years I found distinct fibrosis in 17. Of these 10 were over 40 years of age. (Of the younger cases 2 were due to congenital syphilis, 2 were alcoholic subjects, 1 was a case of diabetes, 1 the case of tuberculosis already mentioned, and 1 a child with Banti's disease.)

The arteries in senile cases are usually the seat of marked sclerosis, and the fibrosis may be looked upon as secondary to atrophy of the secreting cells, due to deficient blood-supply. With degenerative causes of fibrosis we may perhaps include the condition produced by long-continued passive congestion, as in cases of chronic cardiac failure. The exact method of production of this "cyanotic induration" need not be discussed here. The bands of fibrous tissue are often studded with small granules of dark brown or black pigment derived from extravasated blood.

The relation of cancer to fibrosis of the pancreas is of some interest. In cases of malignant disease the gland is almost always the seat of some fibrosis which it is natural to attribute to obstruction of the ducts, or to

the direct irritant action of the developing new growth. On the other hand, there is the possibility that the fibrosis is the primary lesion, and that the new growth originates in some group of cells isolated by the enclosing meshes of the stroma (*vide* case on p. 308).

Age and Sex.—Of 62 reported cases 24 occurred in persons between 20 and 40 years of age, and 33 between 41 and 60. The youngest was a child of 5 (Moynihan). Syphilitic fibrosis is met with in infants and even in the fetus. Opie states that males are more often affected than females, but I find 34 cases recorded in women as against 28 in men. Probably the sexes suffer about equally.

Morbid Anatomy.—In the majority of cases in which microscopical examination shews the pancreas to be the seat of fibrosis, there is little or no indication to the naked eye that anything is amiss. The gland may, however, feel unduly hard, and on section the lobulation may be more marked than usual; individual lobules may even be clearly visible on the surface of the pancreas through its peritoneal covering. The size of the organ varies considerably. In some cases it is much enlarged in all directions, and its weight is much increased: I have elsewhere recorded an instance in which the gland weighed just 1 lb. (454 grms.). In other cases it is shrunken and diminished in weight; and there is then frequently a considerable deposit of fat lying among the lobules; this may be compared with the increased amount of fat found in the hilum of a granular contracted kidney.

Opie has distinguished two varieties of fibrosis of the pancreas, according to the distribution of the fibrous bundles. In the one (interlobar) the increase of connective tissue takes place between the lobes of the gland, being arranged in coarse bands which may be readily visible to the naked eye. In the other (interacinous) the arrangement of the newly formed tissue is in a much closer meshwork, separating individual lobules and acini of the pancreas. Opie states that in the latter variety the fibrous tissue is apt to invade the islands of Langerhans, and that in consequence diabetes is not uncommonly met with in such cases. A close resemblance exists between these varieties of sclerosis in the pancreas and the different forms of cirrhosis of the liver, the interacinous form corresponding with hypertrophic biliary cirrhosis, both in the arrangement of the fibrous tissue and in the increase of size seen in the pancreas as a whole, and the interlobar form being comparable with ordinary multilobular portal cirrhosis and accompanied by shrinking of the pancreas. As in the liver, so here, it is impossible to draw a hard-and-fast line between the two forms of fibrosis: mixed forms occur, and in one and the same pancreas a coarse distribution of the fibrous septa may exist in one part, a finer arrangement in another.

In the more acute cases of interstitial pancreatitis the fibrous septa are richly cellular, consisting of rapidly-growing connective tissue in which many nuclei are visible; whilst in chronic cases the bands of fibrous tissue contain few cells. The origin of the new tissue may be traceable to either the ducts or the blood-vessels by the more marked

development of fibrous tissue round one or other of these systems, but in many cases this distinction is not feasible. The pancreatic cells may look fairly normal or may be shrunken and atrophic: in some cases the arrangement in acini becomes obscured, and in advanced cases single cells may be seen lying in the dense stroma. The occurrence of fatty change has been already mentioned. In many cases of pancreatic fibrosis the change is not equally marked throughout the gland. A case has already been alluded to in which the tail alone was affected (Carnot). Much more often the head of the gland is the seat of sclerosis; this part of the pancreas is then swollen and hard, forming a mass which may even be recognisable in thin subjects by palpation through the abdominal wall. This condition of the pancreas may occlude the biliary duct in its passage to the duodenum, and jaundice is thus produced. The localised swelling and hardness of the head of the pancreas may suggest the existence of a tumour and give rise to an unduly gloomy prognosis. Compression of the portal vein and of the inferior vena cava in a syphilitic case gave rise to ascites and oedema of the legs (Drozda).

Associated pathological conditions which may be met with along with chronic indurative pancreatitis are arteriosclerosis and granular kidney, cirrhosis of the liver, cholecystitis, cholelithiasis, and chronic catarrhal conditions of the duodenum. Cysts of the pancreas may be found along with fibrosis, and are attributed by most writers to retention of secretion behind obstructions formed by the constricting bands of fibrous tissue. Truhart, however, believes almost all pancreatic cysts to be haemorrhagic in origin (see *Cysts*, p. 309). Suppuration and haemorrhage may occur in the diseased glands, and calculi may be found in the ducts. Peritonitis sometimes exists over a localised fibrosis of the pancreas, e.g. over the enlarged head of the gland. The spleen is occasionally enlarged (Guillain, Robson). Fat-necrosis is only rarely met with in cases of chronic pancreatitis: its presence was noted by Opie and by Rixford.

Pathology.—Failure of the pancreas to pour its digestive ferments into the intestine should theoretically affect the absorption alike of proteins, of fats, and of carbohydrates. As a matter of fact the digestion of starch materials seems to be little, if at all, affected, although the subsequent fate of such materials in the body is influenced in some cases by the absence of the internal secretion of the gland, or at all events of some obscure metabolic influence. The digestion of fats is much impaired, as is shewn by the fatty stools characteristic of chronic pancreatitis. It is difficult to distinguish the exact effects due to absence of pancreatic juice on the one hand and of bile on the other: lack of either ingredient may cause some appearance of fat in the faeces. A special sign of defect in steapsin (lipase) in the intestine consists in an alteration in the amounts of neutral fat and of soaps and fatty acids, a much larger proportion of the neutral fat appearing in the stools owing to failure in the normal process of saponification. Normally 75 per cent of the faecal fat is found to be altered in this way: in pancreatic disease

only some 25 per cent is excreted in the form of fatty acid. As a further result of the same condition, it is said that the stools in cases of pancreatic disease are neutral or alkaline, whereas in case of defect of bile they are acid (Monier). This does not hold good invariably, for the faeces in pancreatic affections are sometimes distinctly acid in reaction (Robson). Failure in the digestive trypsin is manifested by defective digestion of meat-fibres, which may appear in large quantities in the faeces, shewing the characteristic striation. Passage of recognisable cellular nuclei in the stools is stated by Schmidt to occur in these cases, the pancreatic juice being the only intestinal ferment capable of breaking up these structures. Normally some 5 per cent of the total nitrogen taken in the food appears in the stools : in pancreatic disease as much as 30 per cent may be thus excreted. The relation of the pancreas to alimentary glycosuria and to diabetes is considered under the heading of diabetes mellitus. It is rare for fibrosis of the pancreas to proceed to such a degree as to destroy the greater part of the secreting tissue : this may, however, occur in some cases, and diabetes will then ensue. Specimens of such a pancreas were kindly sent me by Dr. F. W. Mott, from an insane patient who died with symptoms of severe diabetes : scarcely any glandular elements were discoverable amid the dense fibrous tissue which had taken the place of the original cells. It is said that the islands of Langerhans survive the ordinary acini in cases of fibrosis produced by ligature of the ducts, and sometimes islands are visible in ordinary pancreatitis among the fibrous stroma. The absence of diabetes in most cases of chronic pancreatitis has been thus explained. Opie found that the islands were affected in the interacinous form of fibrosis, not in the interlobular, and believes diabetes to be associated with the former condition. I have, however, found much more advanced fibrosis present in cases in which there was no diabetes than in those associated with this malady (with the exception of the case just quoted). Diabetes may ensue after operation for the pancreatic condition as in Dr. S. Phillips' case, or it may disappear as the result of treatment (Chrzelitzer). In many cases of diabetes no structural change can be seen in the pancreas.

Clinical Phenomena.—The vast majority of cases of fibrosis of the pancreas are only discovered on the post-mortem table : it is clear therefore that mild degrees of the affection can run their course without giving rise to any characteristic symptoms. In such instances there has been sufficient pancreatic tissue left to carry on the digestive and other functions of the gland. In a comparatively small number of cases definite symptoms occur during life, which indicate disease of the pancreas. Sometimes there is an acute onset with epigastric pain and vomiting, pointing to subacute inflammation of the pancreas as the initial condition. In other instances there is gradual emaciation, with increasing weakness and signs of pancreatic insufficiency. These consist of loss of appetite, abdominal discomfort, and alteration in the character of the faeces. The loss of appetite may amount to a positive loathing for food (Moynihan). The motions may be large in amount and pale in colour,

almost resembling the typical colourless evacuations of jaundice ; this appearance apart from icterus was pointed out by Claude Bernard and more recently by Mr. T. J. Walker as denoting pancreatic disease. Chemical and microscopical examination shews the presence in the stools of an increased amount of fat and of undigested muscle-fibres derived from meat. The fat may be so large in amount as to appear as oily drops floating on the surface of the motion, or may only be discoverable by chemical examination.

Many cases of chronic pancreatitis are accompanied by recurrent attacks of epigastric pain. This is severe in character, and arises suddenly without warning. It may be accompanied by vomiting of biliary material. The attacks closely simulate biliary colic, but the pain is chiefly referred to a point a little above the umbilicus and does not usually radiate to the right shoulder. The wasting met with in cases of chronic pancreatitis is often extreme, and may give rise to a suspicion of malignant disease. This may be strengthened by the increasing bodily weakness by which it is accompanied, and by the earthy colour of the skin. Pigmentation of the skin is not common, but is occasionally seen. Salivation occurred in one case (Robson and Cammidge). Mr. Mayo Robson lays stress on the occurrence of attacks of shivering, like ague, as very characteristic of chronic pancreatitis.

Jaundice is usual in severe cases. It may be intermittent at first, but soon becomes permanent and deepens as time passes. It may be accompanied by itching, slowness of the pulse, and mental depression. Small quantities of bile-pigments may be found in the faeces from time to time. The gall-bladder is generally distended, and may contain either normal bile or only clear mucus.

Physical examination may reveal, in addition to the emaciation already described, the existence of resistance, or of a definite tumour, in the region of the pancreas. As the head of the gland is usually most affected, the tumour will lie as a rule just above and to the right of the umbilicus. The tumour may vanish and then reappear (Arnsperger, Barling). There is usually tenderness on pressure in the epigastric or umbilical region. The enlarged gall-bladder may also be palpable, and the edge of the liver is often to be felt below the costal margin. The spleen is not usually recognisable.

The urine is not generally much affected. Allusion has already been made to Mr. Cammidge's "pancreatic reaction," but the constancy of this is doubtful. A trace of albumin is often discoverable in subacute cases, and in chronic instances in which there has been great diminution in the secretory powers of the gland there may be glycosuria ; the latter is, however, rare. Intermittent glycosuria was noted by Allen, and was present in a case of haemochromatosis with marked pancreatic fibrosis which I have recorded elsewhere. Maltose is occasionally present instead of glucose. Fat has been seen in the urine (lipuria) by Mr. Mayo Robson in one case, and a case of fatty ascites recorded by Gaultier is attributed by this author to pancreatic disease. Mr.

Cammidge found the excretion of oxalic acid increased in chronic pancreatitis, and that crystals of calcium oxalate were often present in the urine.

Diagnosis.—The diagnosis of chronic pancreatitis falls into two parts, viz. the recognition (*a*) of the existence of some affection of the pancreas and (*b*) of the nature of the condition present. The existence of digestive disturbances such as anorexia, nausea, constipation, or diarrhoea, along with progressive emaciation and increasing weakness, should suggest the possibility of pancreatic disease. A careful examination of the stools should then be made for undigested fat and muscle-fibres. Should these be found the probability of the pancreas being at fault is much increased. The urine should then be examined by Mr. Cammidge's method ; and whilst the absence of the characteristic reaction is probably of little importance, the discovery of the crystals will at all events strengthen the grounds for a positive diagnosis. Glycosuria is confirmatory evidence ; its absence is of no value as a negative indication.

In all cases of persistent jaundice the possibility that the pancreas is the seat of disease must be considered. Other causes of such a condition are impacted gall-stones, stricture of the bile-duct (simple or malignant), and diseases of the liver (cancer, biliary cirrhosis). These last are generally accompanied by considerable enlargement of the liver. In the case of gall-stones there is usually an abrupt onset with acute radiating pain. The attacks of pain met with in chronic pancreatic disease may, however, closely resemble this. It is stated that impaction of a gall-stone in the common duct is almost invariably followed by shrinking of the gall-bladder, whereas in jaundice due to other causes the gall-bladder is generally distended. (Courvoisier's law, Bard-Pic syndrome.) The existence therefore of a palpable tumour in the region of the gall-bladder is against the presence of an impacted gall-stone. A gradual onset of jaundice is in favour of pancreatic disease, if such conditions as simple catarrhal jaundice can be excluded.

When the existence of some affection of the pancreas has been rendered probable on such grounds as have just been indicated, the question arises as to the exact condition which is causing the symptoms. Not only chronic interstitial pancreatitis, but also cancer of the pancreas, is capable of giving rise to this train of phenomena—emaciation, weakness, jaundice, fatty stools, and a palpable tumour in the epigastric region. In many cases diagnosis is impossible. The age of the patient may be of importance, cancer being unusual in persons under forty years of age. Acute pain is not common in this disease in its early stages, whereas attacks of pain are frequent in pancreatitis. The larger the tumour, the more likely is it to be malignant ; rapid growth or alteration in consistency would favour the same diagnosis. Mr. Robson and Mr. Cammidge state that the proportion of fat in the stools is greater in cases of cancer (averaging 77 per cent) than in simple chronic pancreatitis (average, 60 per cent). In biliary obstruction alone the absorption of fat is much less defective (see also Cancer of Pancreas, p. 306).

Several special tests have been devised to ascertain the functional condition of the pancreas. Thus, Sahli recommends the administration of iodoform in glutoid capsules hardened in formalin, this material not being dissolved by the gastric juice : if iodine does not appear in the urine within six to eight hours, the pancreas is, he considers, defective. The value of the procedure is doubtful : defect in the motor function of the stomach may obviously give rise to mistakes, and sometimes in normal persons the appearance of the iodine in the urine is delayed. The existence of alimentary glycosuria has been supposed to point to pancreatic insufficiency. To investigate the question of its presence in any case, 100 grams (about $3\frac{1}{4}$ oz.) of grape-sugar are administered, and sugar is looked for in the urine during the next twenty-four hours. This phenomenon, however, is not at present satisfactorily established as a sign of pancreatic insufficiency. In order to make certain of the existence of excess of fat in the stools it is well to put the patient on a diet containing a definite quantity of fat, as healthy persons may pass some amount of fat when living on a diet containing too much of this substance. For this purpose special diets are employed : thus, Gaultier gives 100 grams of bread, 60 grams lean beef, 20-30 grams butter, 300-500 c.c. milk, and 100 grams potatoes for a test meal, whilst Baumstark recommends $1\frac{1}{2}$ litres of milk, 100 grams rusks, 2 eggs, 50 grams butter, 125 grams minced beef, 1900 grams potatoes, and 80 grams oatmeal as a day's allowance.

For the performance of Schmidt's test for failure in digestion of nuclei, little cubes of beef are prepared, which are hardened in absolute alcohol and kept in spirit. They are administered in little silk bags, which are sought for in the stools. In order that the test may be fair, the material must not remain in the alimentary canal more than thirty hours : on the other hand it must not be unduly hurried through. Sections of the cubes, when recovered from the faeces, must be cut and stained and examined with the microscope.

Prognosis.—Chronic pancreatitis is a rare cause of death directly, but it is not unlikely to lead to diabetes and thus prove fatal. Consequently it is important to relieve the condition as soon as possible before irreparable mischief has been done. Of the exact prospects of relief by surgical operation it is difficult to speak dogmatically. Of recorded cases the great majority have been successful so far as immediate results were concerned. Thus, I find 35 cases of operation for chronic pancreatitis recorded, with 29 recoveries and 6 deaths. The figures are probably, however, misleading, as successful cases are likely to be published and unsuccessful issues consigned to oblivion. In one of Mr. E. Owen's cases the abdomen was opened and nothing further done ; yet the patient recovered speedily. In his second case the immediate result was successful, but the patient was subsequently reported as not doing well. Arnsperger and Dr. Phillips both record instances in which death took place a year later, and in Barth's case a second operation was necessary and proved fatal from uncontrollable

vomiting. Diabetes may follow in spite of operation if the pancreas be extensively damaged.

Treatment.—The great question in regard to the treatment of chronic pancreatitis is that of the advisability of surgical interference. The class of case in which the question of operation arises is that in which there is long-continuing jaundice, and here the condition present may be either chronic pancreatitis, cancer of the head of the gland, or impacted gall-stone. In every case of continued jaundice in which there is a possibility that the cause of the condition is an impacted gall-stone, operation is certainly the proper course to adopt. The question, however, remains as to the correct procedure in cases in which chronic pancreatitis is recognised to be present. It is certain that this condition may subside without interference, as in Mr. E. Owen's case, in which the abdomen was opened and closed again without interference with the pancreas or bile-passages. At the same time it is clear that the obstruction caused by enlargement of the pancreas may be prolonged for an indefinite time, and that during this period the patient is likely to be passing into a more and more emaciated and debilitated state. Operation, on the other hand, offers the prospect of a much more rapid recovery, and the actual risk run is not, in skilful hands, very great (see p. 264). Again, if cancer of the pancreas be present the ultimate fatal issue is certain, and in the most unfavourable event operation can but forestall it by a few weeks. In judging of the time at which operation may therefore be advised, it must be borne in mind that it is not very unusual for jaundice, even in those favourable cases which are usually classed as catarrhal, to last for several weeks before it clears up. Hence patience must be exercised. The duration of waiting must vary in different cases according to the state of the patient, but not less than six weeks should be allowed to elapse if there is no rapid loss of strength and weight or other symptoms of dangerous toxæmia.

If operation be decided upon, two procedures are available. The simplest method of draining the biliary passages is by the creation of an external fistula (*cholecystostomy*): this has the advantage of facility and comparative freedom from risk, but is open to the theoretical objection that the opening may close and leave the patient as badly off as before. The alternative procedure is the formation of a permanent passage between the gall-bladder and the intestine (*cholecystenterostomy*). This involves a more serious operation and consequently greater risk. Instances are also recorded in which the artificial opening has closed up in course of time. No general rule can be laid down as to the comparative values of the two methods, which must be determined by the operator in individual cases. Mr. Mayo Robson recommends the more radical treatment. Very favourable results are, however, reported after the simpler procedure, and as there is reason to hope that the inflammatory condition of the pancreas will subside fairly rapidly when drainage has been effected, the liability of the external fistula to close up earlier does not seem a serious contra-indication to this operation.

In cases due to syphilis appropriate treatment with mercury and iodide of potassium may prove effective, as in a case of Chrzelitzer's. Otherwise measures should be adopted to subdue any duodenal catarrh which may be maintaining inflammation in the pancreatic ducts; salicylate of bismuth is a useful remedy for this purpose, and urotropine may be given with a view to disinfecting the biliary passages. To improve the digestion preparations of the pancreas may be employed. Good results were obtained by Fles (1864) in a case of diabetes with fatty stools from the administration of fresh pancreatic tissue. Weintraud employed pancreatin with advantage, the digestion of meat being improved, whilst that of fat was little influenced. A more recent preparation, pancreon, in which the pancreatic extract is combined with tannin, so as to be insoluble in the gastric juice but liberated in an alkaline medium, seems to offer some advantages.

AFFECTIONS OF THE ISLANDS OF LANGERHANS.—It may be convenient to group together the affections to which the islands of Langerhans are liable. The origin and nature of these formations cannot be here discussed. They are said on the one hand to arise developmentally from the pancreatic rudiments, but to take on special characters at an early period. On the other hand, the appearances which they present in the human pancreas suggest that they are continually being formed from the secreting cells. Lagesse holds that they can change back again into acini. The persistence of the islands in cases of fibrosis and fatty degeneration of the pancreas, due to ligature of the ducts, is remarkable; but the possibility that such acini as persist take on the appearance of islands must at least be considered.

The most characteristic morbid change in the islands of Langerhans is the *hyaline degeneration* which has been described as occurring in them in cases of diabetes mellitus. The walls of the capillary vessels forming a meshwork in the island become swollen and homogeneous in appearance, and the cells of the island disappear proportionately. Opie describes the change as extending into the cells of the islands, many of which are converted partially or almost entirely into hyaline material. In earlier stages individual cells may contain particles of hyaline matter. The change thus closely resembles that in amyloid disease. The condition is rare in diabetes and it is doubtful whether it occurs apart from this disease: it is said to do so by Carnot and others. It does not seem certain that all forms of hyaline change in the islands are in reality one and the same. Homogeneous masses produced by degeneration of the cells of the island, and presenting a hyaline appearance, are met with in connexion with arteriosclerosis, and hyaline masses of extravasated blood-clot also occur.

Punctiform haemorrhages into the islands are quite common; I have found them in some 5 per cent of the cases which I have examined, and a more extended investigation would probably have revealed other instances. Fatty degeneration of islands is not often recognisable, but

in one or two instances I have seen a round vacuole in an island clearly representing a dissolved globule of fat. *Vacuolation* of the islands has been described as one of the conditions met with in diabetes, but the arrangement of the insular cells varies so much in different specimens that it is difficult to fix definite limits beyond which looseness of texture becomes pathological. Schmidt has recorded a case in which the islands were the seat of a small-celled infiltration, the rest of the pancreas being unaffected; this appears to be a unique observation. Ssobolew found in a case of diabetes a hypertrophy of some of the islands of Langerhans, which he regarded as compensatory for the disappearance of many of the other islands which had taken place. These cell-groups are usually numerous and large in children; they are said to undergo enlargement in infective diseases, though I have not been able to satisfy myself as to this effect. Carnot states that the islands are increased in poisoning by arsenic and phosphorus. In normal circumstances they vary greatly in size and shape.

It is not very uncommon to find groups of eight or ten islands lying together in the meshes of a fibrous reticulum: sometimes fifteen or twenty are thus arranged. These groups often contain a certain proportion of alveolar spaces lined with columnar epithelium, which seem either to represent islands which have degenerated into this condition or outgrowths from the ducts which are destined to develop into islands. In other cases groups of channels with columnar lining cells occur, at first sight resembling very closely the adenomas met with in the breast. They usually lie in the neighbourhood of ducts, and in one case I was able to trace the origin of a system of tubular outgrowths to a large duct. As the pancreas originally develops by the budding off of tubular outgrowths from the primitive ducts, it seems probable that the "adenomatous" formations may represent attempts at reproduction of glandular tissue,—of which possibly islands may be a developmental stage,—or at all events a new formation of islands. Herxheimer speaks of new formation of islands from small ducts as characteristic of diabetes.

Fabozzi, as the result of a study of several cases of carcinoma of the pancreas, concluded that this affection may originate in the islands of Langerhans, but the illustrations given in his paper are not conclusive, and his views have been opposed by Reitmann and by Grimani. Sauerbeck in one case, which appears to have been a pathological curiosity, found metastatic deposits from a mammary cancer lying in the islands. Nichols has described an adenoma arising from an island, and a similar formation was found by Helmholz; in the latter's case the growth consisted of anastomosing masses of cells, resembling those of the islands, lying in a stroma richly supplied with capillaries. The growth was about 5 mm. in diameter.

ATROPHY.—Some degree of atrophy of the secreting cells of the pancreas is probably common after middle age, and precedes the fibrosis already described as representing a senile change. In starvation the

cells of the gland become small and shrunken, even the nuclei being diminished in size according to Jarotzky, and a somewhat similar atrophy may be seen in some cases of advanced arteriosclerosis and in infantile marasmus. As in other organs fatty change often accompanies the wasting. Hansemann distinguished two forms of atrophy of the pancreas :—(1) simple wasting of the cells of the acini, and (2) atrophy with concomitant fibrosis. The first occurs in cases of general failure of nutrition and may be called "cachectic atrophy." The pancreas thus affected presents a rounded, almost cylindrical form, and is of normal consistency. It is easily separable from surrounding structures, and hence can be readily removed from the body after death. The cells and lobules are shrunken, but the gland is not pigmented or fibrotic. In the second form the pancreas is soft in consistency and dark in colour. It is flattened from before backwards, and is firmly adherent to surrounding structures. The gland is penetrated by an increased amount of fibrous tissue, and there may be evidence of cellular proliferation or infiltration in the presence of an increased number of round cells. This latter form of atrophy is associated with diabetes. The condition is somewhat analogous to that found in the granular contracted kidney, which is likewise often closely adherent to surrounding parts. Both are often associated with arteriosclerotic changes. In two cases of diabetes mellitus occurring in young persons (brothers) I found marked atrophy of the pancreases, the gland weighing in one case $1\frac{1}{4}$ oz. and in the other 1 oz. In one case there was no apparent increase of fibrous tissue, in the other a very insignificant amount.

FATTY CHANGE.—The existence of some amount of fat among the lobules of the pancreas is very common, if not almost invariable, in persons over forty years of age. Hence it is difficult to fix a limit above which fatty change may be considered pathological in amount. In 100 glands from consecutive (unselected) necropsies I found well-marked fatty change ten times. Arteriosclerosis is a common accompanying, and probably causal, condition. Some degree of fibrosis is also frequent along with the steatosis. In obese persons the gland is usually penetrated by layers of fat lying between the lobules, and in advanced cases almost all the secreting tissue may be replaced by fat. In some cases of diabetes fatty change of the pancreas has been the sole recognisable affection.

AMYLOID CHANGE is frequently demonstrable in the blood-vessels of the pancreas in cases of generalised amyloid disease; of 3 cases upon which I made necropsies, it was present in every one, when examined microscopically after staining with gentian violet. The change is not often sufficiently advanced in this organ to be recognisable with the naked eye or to affect the general consistency of the gland.

PIGMENTATION.—Deposits of small particles of dark pigment are not uncommon in the pancreases of those who have died of cardiac failure. They lie in the connective tissue and are most marked in the neighbourhood of blood-vessels. The pigment represents the remains of haemo-

globin derived from blood-corpuscles which have escaped from the vessels owing to past congestion. In the disease known as haemochromatosis or bronzed diabetes the pancreas as well as the liver and other organs may be the seat of a deposit of pigment. Two separate substances have been identified by Auscher and Lapicque, a brown material which contains iron and is said to be ferric hydrate, and a black substance which is free from iron and may be a melanin. The pancreas in this disease is fibrous and the liver is usually cirrhotic. The condition is probably a toxæmia with destruction of the red corpuscles of the blood.

Cloudy Swelling or granular degeneration is found in the cells of the pancreas as in other organs after death from infective febrile diseases.

FAT-NECROSIS.—The first complete description of this condition was given by Balser in 1882, though the phenomena had been observed previously by Schmidt in 1818, and after him by Rokitansky, Virchow, and others: indeed, Truhart traces a reference to this necrosis in the writings of Greisel in 1673. The pathology of the condition was carefully investigated by Langerhans in 1890. In recent years valuable light has been thrown on the origin and nature of the condition by the experimental investigations of Hildebrand, Dettmer, Körte, Williams, and Flexner.

Description.—In a well-marked case of disseminated fat-necrosis there are seen, on opening the abdomen either during life at a surgical operation or at an autopsy, scattered over the peritoneal surface a number of small, opaque, whitish points or specks. These vary in size from 0·5 to 5 mm. in diameter, and may be arranged in groups or lines. They are usually most numerous in the fat of the mesentery and in the retroperitoneal fat around the pancreas. Not infrequently, on incising the pancreas, white points are discoverable among the acini of the gland, even when none are discernible in the surrounding parts. Occasionally the small white areas coalesce into larger patches, and rarely large masses of fat undergo necrosis *en masse*. On making a section of one of the small areas with a knife, it is seen that the process extends a little way below the surface, being bounded by a semicircular arc on its deep aspect. The opaque material is cheesy or soapy in consistency, and can be readily scraped out with the tip of the knife. The necrosed patches are usually sharply defined and appear embedded in normal fat. In some cases, however, they are surrounded by a red zone of haemorrhage. Microscopically, the central portion of a necrosed area consists of structureless debris, many of the granules of which stain deeply with haematoxylin. Outside this is a zone of cells almost completely destroyed, their places being occupied by shrunken remnants of their capsules, or by hyaline masses, round or angular in shape. These masses dissolve in sulphuric acid, leaving a granular residue of calcium sulphate; they consist of a compound of calcium with fatty acid (calcium stearate, oleate, etc.). At the periphery of the area are cells with granular contents, many of which contain sheaves or stars of needle-shaped crystals, somewhat resembling those of tyrosine. Strands of connective tissue run through the necrosed mass, and similar

bundles may form its boundaries. The surrounding fat may be found infiltrated with red blood-corpuscles, or aggregations of leucocytes may be seen at the margin of the necrosed tissue. The latter often contain particles of fat or of calcium salts of the fatty acids. A special staining-reaction for fat-necrosis was devised by Benda. The reagent is that employed by Weigert as a mordant for neuroglia, and consists of a solution of copper acetate and chrome-alum with acetic acid. If portions of necrotic fat are stained with this dye they are coloured a vivid green, "as if smeared with verdigris," while the normal tissue around presents only a faint greyish-green tint. The colour depends on the interaction of copper acetate with oleic acid. Benda and his pupil Liepmann hold that the reaction is characteristic of intra-vitam necroses, but Thorel points out that nothing more than the presence of free oleic acid or calcium oleate is indicated, and that fat digested by post-mortem action of pancreatic juice will give the same colour.

Etiology and Pathology.—Much controversy has taken place as to the causation of fat-necrosis on the one hand, and as to its relation to accompanying clinical phenomena on the other. Balser, who first noted the condition in fat subjects, originally held that it was a direct result of overgrowth of fat, some portions of the hypertrophied adipose tissue failing to receive adequate nourishment, and consequently undergoing necrosis. The investigations of Langerhans first brought to light the essential nature of the process at work, namely, a saponification or splitting up of the fat into its constituent elements, glycerin and a fatty acid. A ferment, steapsin or lipase, being known to exist in the pancreatic juice, it was natural to associate the necrosis with this agent. In favour of this explanation are the facts that fat-necrosis is often seen in the substance of the pancreas when it is absent elsewhere; that in cases of disseminated necrosis the lesion is most marked in the neighbourhood of the pancreas, which may be surrounded by masses of necrotic fat; and that fat-necrosis is common in disease of the pancreas, and exceedingly rare apart from recognisable affection of this organ. Thus, among 94 cases of pancreatic haemorrhage fat-necrosis was recorded as present 57 times (60 per cent). Among 46 cases of suppuration it occurred 25 times (54 per cent); among 33 cases of acute inflammation 13 times (39 per cent); among 17 cases of necrosis 12 times (70 per cent). These figures are probably below the truth, since in many recorded cases no mention is made of fat-necrosis, which was probably not sought for. In only a minute proportion of the records is its absence noted. In cases of chronic pancreatitis fat-necrosis is rare, but cases are recorded by Opie and by Rixford.

Experimental evidence supports the view that the pancreatic juice is the cause of fat-necrosis. Thus, Langerhans produced this condition by injecting a fluid obtained by crushing fresh pancreas with powdered glass; Jung by implanting pieces of pancreas, freshly excised, in the adipose tissue; Hildebrand by causing obstruction of the pancreatic secretion. That the fat-splitting ferment of the pancreas is the causal agent is shewn by the experiments of Dettmer, who obtained fat-necrosis by injection of

pancreatic extract, but not with trypsin alone, as well as by the discovery of Flexner that lipase is demonstrable in the patches of necrosis if they are examined at a sufficiently early stage. Injuries to the pancreas are frequently followed by this lesion, and experimental injuries were invariably followed, in the hands of Katz and Winkler, by some degree of necrosis. Injection into the pancreas of hydrochloric acid, sodium hydrate, or formalin, has a similar effect (Flexner). Lipase may be detected in the urine in some cases of pancreatic lesions (Hewlett). Two great objections have been raised against the acceptance of the pancreatic view of the causation of fat-necrosis:—(1) That cases occur in which there is no demonstrable lesion of the gland; and (2) that some foci of necrosis are at such a distance from the pancreas that it is almost inconceivable that the digestive ferment can have been carried there in sufficient quantity to produce saponification of the fat. (1) Cases are recorded by Chiari, Wulff, Haffner, Ostermaier, Wiesinger, and others, in which extensive fat-necrosis was present, but the pancreas was apparently healthy. In some of these, however, no microscopical examination of the gland was made, as in Ostermaier's case, in which there was yet to the naked eye some increase of interstitial tissue, and in Wiesinger's, in which recovery occurred. In others there was blood in the general peritoneal cavity, but the source of the haemorrhage was not determined; hence it is not unlikely that some small lesion of the surface of the pancreas may have existed, which might easily elude observation. (2) Foci of necrosis in such parts as the sub-epicardial fat, the subcutaneous panniculus adiposus, and the medulla of bone seem at first sight to negative a pancreatic origin. Truhart believes that fat-necrosis is produced by direct carriage of the ferment by the lymphatics, and holds that its passage through the diaphragm is not difficult. He believes that it may even reach the subcutaneous tissue over the abdomen by digesting the peritoneum and finding its way to the surface. An ingenious explanation of the occurrence of necrosis in distant parts, which is capable of explaining the rare appearance of necrosis in the bony medulla, is put forward by Payr and Martina, who believe that embolism by pancreatic cells may occur. They have found such cells in the veins after experimental injury to the gland. In this way the not infrequent foci of necrosis in the liver in conjunction with pancreatic disease may also be explained. Flexner considered that the lesions in the bones must be due to some other cause than those around the pancreas, and invoked the aid of micro-organisms.

That time is needed for the appearance of fat-necrosis is shewn by the observations of Simmonds and of Kindt, who found at operations for pancreatic injuries that no fat-necrosis was present, whereas at the subsequent autopsies the lesion was well marked. In Kindt's case an interval of 98 hours had elapsed; in Simmonds' 34 hours. Complete recovery may take place, as in Wiesinger's case, in which the abdominal fat was found normal at a subsequent operation.

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TUMOURS ; CYSTS ; CALCULI ; TUBERCULOSIS ; SYPHILIS

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TUMOURS.—Morbid Anatomy.—Solid tumours of the pancreas are very uncommon ; carcinoma, sarcoma, lymphadenoma, adenoma, tuberculosis, and gumma all occur, but, except carcinoma, are so excessively rare as to be of very little clinical importance. Writers differ as to the frequency with which carcinoma occurs. The experience at Guy's Hospital (43) confirms the general opinion that primary carcinoma is at least twice as common as secondary growths ; but a few authors (Oser, Leo) hold the contrary opinion. When not primary, malignant disease of the pancreas is more often due to direct extension from a neighbouring organ than to metastasis from a distance. At Guy's Hospital carcinoma of the pancreas occurs in about 0·55 per cent of 11,000 autopsies, whilst Biach's figures give a percentage of 0·12 only out of 23,611. Males are affected three times as frequently as females. Two-thirds of the cases occur between

the ages of forty and sixty ; the ages at the time of death of 60 cases were distributed as follows :—Under thirty, 2 cases ; between thirty-one and forty, 5 ; between forty-one and fifty, 17 ; between fifty-one and sixty, 23 ; between sixty-one and seventy, 11 ; and over seventy, 2. Kühn has seen a cubical-celled carcinoma in a child aged two years.

In most instances the growth is the hard form of carcinoma, the soft or encephaloid form being rare. Histologically the structure is either a spheroidal- or a columnar-celled carcinoma, more frequently the former; colloid carcinoma is very unusual. In 60 per cent of the cases the growth starts in the head of the pancreas ; in 30 per cent it is diffuse ; and in the remainder either the tail or the body is the part most affected. (For carcinoma originating in the islands of Langerhans, see p. 297.)

In most cases in which the growth starts in the head, the duct is sooner or later completely obstructed, and according to Boldt, in about a third of these cases the distal part of the duct becomes dilated ; in some cases a retention-cyst forms in the tail. When the growth invades the end of the duct of Wirsung and the ampulla of Vater, it also produces obstruction of the common bile-duct with distension of the gall-bladder, enlargement of the liver, and severe, progressive, and permanent but painless jaundice, extreme emaciation, and a rapid cachexia (Bard and Pic). The bile-duct runs through the head of the pancreas in two-thirds of the bodies examined, and in the remaining third behind the organ ; hence in the former condition a growth in the head of the pancreas readily induces jaundice, but not in the latter. The tumour varies in size, and is generally smaller than an orange. When the growth starts in the body there will probably be intense pain, with rapid cachexia and bronzing of the skin (Lancereaux). On section the colour varies according to the amount of fibrous tissue, the extent of the degeneration, the amount of haemorrhage which has taken place, and the presence or absence of bile pigment. The growth may invade the peritoneum and set up adhesions between the pancreas and adjacent organs, such as the stomach, colon, small intestine, spleen, liver, and gall-bladder, but more particularly the duodenum. In nearly half the cases secondary growths occur in the adjacent lymphatic glands in the portal fissure and along the aorta, and in more than a third in the liver. In one-third of the cases there is ascites due to malignant peritonitis, and this may obscure the existence of a pancreatic lesion. Occasionally the growth fungates into either the stomach or the duodenum, and in the latter position may lead to obstruction, either by pressure or by causing a kink. Less frequently metastases occur in the spleen, kidneys, abdominal wall, and distant viscera. In 71 cases of primary carcinoma of the pancreas there were metastases in glands in 29 cases, in the liver in 43, in the peritoneum in 16, in the lungs in 12, in the pleura in 7, and in other organs in 1 or 2 only. The rarity of pancreatic calculi in carcinoma of the pancreas contrasts with the close association of gall-stones and primary carcinoma of the gall-bladder.

Malignant disease may originate in the termination of Wirsung's duct close to the ampulla of Vater, but this has been but rarely recorded, and the diagnosis from carcinoma starting in the glandular acini of the head of the pancreas cannot generally be made. Letulle and Verliac, who refer to seven examples, record the following case: A woman, aged sixty-eight years, was admitted with jaundice of five months' duration, preceded by a rigor. The motions were pale, and she presented loss of appetite, rapid wasting, and occasional attacks of colic; the liver was enlarged, hard, and painless, and the gall-bladder distended: a fortnight later she died with colic and diarrhoea. At the autopsy the gall-bladder was distended with bile, and the liver contained suppurating bile-stained cavities. The pancreas was atrophied and indurated, Wirsung's duct was dilated, and the ampulla of Vater was blocked at the entrance of the duct of Wirsung by a nodule of spheroidal-celled carcinoma partially occluding the bile-duct by pressure. Carnot and Harvier record another case. (For primary carcinoma of the ampulla of Vater, see Vol. III. p. 578.)

Primary sarcoma is very rare; about a dozen cases are on record; at Guy's Hospital about one case occurs in every five thousand autopsies. It is rapidly fatal and may occur early in life. In one case a small round-celled sarcoma originated in the pancreas in a man aged twenty-eight. In a woman aged fifty-three there was a diffuse large-celled sarcoma in the pancreas with extensive growth in the glands, stomach, and chest-wall. Secondary sarcoma may occur in the pancreas; it is often melanotic, the primary growth being generally in the uveal tract of the eye; these cases usually run a rapid course.

Secondary growths in the pancreas are of comparatively little importance clinically, as they are not infrequently small; a palpable tumour is six times more likely to be primary than secondary. The primary growth is usually in the stomach, duodenum, or gall-bladder; but even at the autopsy it may be difficult to be certain as to the primary seat. Out of 15 cases of secondary growths in the pancreas, the primary were distributed as follows: stomach 5, oesophagus 4, gall-bladder 2, breast 2, duodenum 1, caecum 1.

Non-malignant Tumours.—About 5 cases of adenoma have been published; the growth consists of a nodule of encapsulated glandular tissue. From the small size of the cells and their large nuclei in his case, Nichols concluded that the adenoma originated in an island of Langerhans. Implication of the pancreas by lymphadenoma has seldom been recorded; this condition was found in 3 cases at Guy's Hospital, but gave rise to no symptoms. In a man aged seventy-seven, who died with lymphatic leukaemia, a small cyst was found in the tail of the pancreas, with a mass near it half an inch across.

The **symptoms** of carcinoma of the pancreas vary considerably, and in some cases, especially in those discovered accidentally after death, are not indicative of their primary seat. In the majority, however, there is a history of digestive disturbance, such as loss of appetite with especial

distaste for meat and fat, flatulence, nausea, discomfort, and vomiting which may be so severe as to cause death. Lesions of the pancreas are especially apt to induce a haemorrhagic condition. The vomit may consist of altered blood, and occasionally there may be severe haematemesis. There is notable loss of weight and general malaise, but the symptoms of pancreatic diabetes, such as hunger, thirst, and glycosuria, are rarely present. Most cases run their course with little or no pain; but when the growth is large or rapid there may be paroxysms of pain extending from the epigastrum to the back, especially to the angle of the left scapula, and not infrequently these are at first thought to be due to lumbago. Pancreatic pain is referred to a point an inch or so above and to the right of the umbilicus. Exceptionally the pain may be agonising, apparently from impaction of the semilunar ganglia, and is sometimes more frequent at night. There is usually jaundice, due to pressure of the growth on the common bile-duct; it may appear suddenly or gradually, is progressive, persistent, and becomes extreme in degree, so that the skin presents a dark, mahogany-brown colour, often with a greenish tint, and is much more extreme than that due to gall-stones. As a result of the obstruction, the liver enlarges and the gall-bladder and ducts become distended. Even when the pancreas is enlarged, it is by no means always readily felt, partly on account of ascites, partly from the prominence of other masses of growth. In nearly half the cases the growth forms a tumour palpable during life; it usually appears just above the umbilicus, and may vary considerably in size. In a few persons who are thin or have a flaccid abdomen the normal pancreas can be felt, and in these circumstances even a small tumour could be detected. In many cases, however, the palpable mass is largely formed by the distended gall-bladder, or by growth in the liver or in the adjacent organs, and is by no means necessarily the pancreatic tumour. The tumour is a deep-seated, rounded, often nodular swelling, which may be tender to the touch, and from its position behind the stomach its definiteness will vary from time to time according to the condition of the overlying viscera. It is but slightly mobile, and moves but little with respiration; pulsation transmitted from the aorta is quite common, but it is not expansile. As the growth is usually in the head of the pancreas, it may interfere with the portal vein or the inferior vena cava and cause ascites or oedema of the legs. In some cases the mass presses upon the pyloric portion of the stomach or on the duodenum, thus producing dilatation of the stomach, and in a few cases it invades their walls. The regularity of the bowels is usually disturbed, resulting in either constipation or diarrhoea. The most striking features about the faeces are their pale, soft, bulky, and offensive character, and the great excess of fat. The pale and oily condition of the semi-fluid motions in pancreatic disease, first described by Bright in 1832, is due to an excess of undigested fat, and analysis shews that the percentage of neutral fat is also increased, since in the absence of steapsin fatty acids are not liberated. Whilst in health 89 to 93 per cent of the fat taken is absorbed,

Müller pointed out that in the absence of bile from the intestine, only 25 to 45 per cent of the fat was absorbed, and that when the duct of Wirsung was obstructed and the pancreas was degenerated, the normal quantity of fat was absorbed, but only 40 per cent of the fat was split into fatty acids and soaps instead of the normal 84 per cent. The presence on microscopical examination of undigested muscle-fibres is, in the absence of diarrhoea, of great diagnostic importance, as this condition was found by Mr. Mayo Robson in 20 out of 24 cases of carcinoma, and in only 16 out of 56 cases of chronic pancreatitis. The reaction of the faeces is often acid. According to Mr. Cammidge the urine fails to give the "C" pancreatic action, except in the few cases with concomitant chronic pancreatitis. When there is well-marked jaundice, due to complete obstruction of the common bile-duct, no stercobilin can be detected in the motions, thus differing from the condition in jaundice due to gall-stones, in which the motions always contain a small amount of pigment. Prof. B. Moore and others have shewn that there is either no free hydrochloric acid or only a very small amount in the stomach contents after a test meal when there is malignant disease of any part of the body, and that this absence or diminution of hydrochloric acid is not confined to cases of malignant disease of the stomach (*vide Vol. III. p. 502*).

The duration of the disease rarely exceeds a year from the first symptom, or six to eight months from the onset of the jaundice; the cachexia steadily increases, the anaemia becomes more profound, and the patient dies from exhaustion.

The diagnosis of carcinoma of the head of the pancreas can generally be made in a characteristic case, such as a previously healthy, middle-aged patient who has wasted rapidly and lost strength, become deeply jaundiced without any pain, and whose gall-bladder is so distended as to form a palpable tumour. This is confirmed if a mass gradually become palpable at or above the umbilicus. In some instances, however, the symptoms are extremely deceptive; thus, the growth may extend into the stomach or duodenum and set up more or less obstruction. The following case illustrates this group of cases: A man, aged forty-five, was admitted with vomiting, haematemesis, and pain above the umbilicus. His stomach was dilated, its contents contained no hydrochloric acid, and there was a tumour palpable between the umbilicus and the ensiform cartilage. Gastro-jejunostomy was performed, and he died a month later. A carcinoma in the head of the pancreas had invaded both stomach and duodenum and obstructed the stomach by kinking. In 20 per cent of the cases the peritoneum is involved and in 10 per cent the pleurae, hence the main sign may be ascites or pleural effusion. In cases such as the following a correct diagnosis is almost impossible: A man, aged sixty-two, was admitted under my care with oedema, cough, dyspnoea, and the physical signs of bronchitis and left pleuritic effusion. At the autopsy the pancreas was much wasted and contained a carcinomatous growth an inch across, about an inch from the head of the pancreas. There was a diffuse layer of growth between the liver and diaphragm.

The following is an example of carcinoma supervening on fibrosis of the pancreas : A man, aged twenty-three years, had suffered from diabetes for seven months ; at the necropsy the pancreas was small as a whole, shewed interstitial fibrosis microscopically, and to the naked eye dense fibrous tracts, areas of fat-necrosis, an abscess 1 cm. in diameter, and enlargement of the tail by a hard carcinoma.

The diagnosis must be made from interstitial pancreatitis, from catarrh, cholelithiasis, and malignant disease of the common bile-duct, and from malignant disease of the pylorus, liver, and the retro-peritoneal space. In *interstitial pancreatitis* the history is much longer, the wasting less marked, there is more tenderness above the umbilicus, and more often a history of attacks of pain. The condition is commonly associated with a stone in the common duct, hence the jaundice is not so complete, febrile attacks due to infection are frequent, and the gall-bladder is less often enlarged. When at an operation for gall-stones an enlargement of the head of the pancreas can be felt there is always a probability that with the removal of the stone the pancreatic condition will clear up. In *catarrh of the common bile-duct* the symptoms are very slight ; the jaundice is of short duration, moderate, and painless. In *common-duct cholelithiasis* there is a history of gall-stone attacks, the jaundice is not complete, and is preceded by pain ; there is tenderness above and to the right of the umbilicus with pain passing to the right scapula, the right rectus is rigid and the abdomen tender, the jaundice is not complete, and there is evidence of infection with rigors and pyrexia. *Carcinoma of the common bile-duct* may be associated with a history of gall-stones, and is generally indistinguishable from that of the head of the pancreas. It is rare, and if the pancreatic duct escapes, the wasting will be less rapid.

In *cancer of the pylorus*, which may be associated with growth in the head of the pancreas, there will probably be more distension of the stomach and more vomiting, but when there is marked jaundice it may be indistinguishable.

Cancer of the Liver.—The jaundice is less marked, and the liver may be obviously infiltrated with nodules of growth and be enlarged.

Treatment is purely palliative, and experience has shewn that operation is not advisable, as it often accelerates the fatal end. In some cases in which exploratory laparotomy was undertaken a cholecystenterostomy has been performed to relieve the jaundice and cholaemia, but the patient has but rarely survived for more than a short time. Mr. Mayo Robson's statistics are as follows : Out of 15 cases in which the gall-bladder was drained, 8 recovered from the operation with an average survival of four months ; of 6 cholecystenterostomies, 2 recovered, with an average duration of a few weeks ; only 4 out of 6 recovered from a simple exploratory operation. Murphy shewed that the mortality of cholecystenterostomy up to 1897 was 83 per cent for malignant disease as against 4 per cent for non-malignant cases. Pain should be relieved by morphine and other sedatives. Haemorrhagic oozing can be most satisfactorily checked by calcium chloride or lactate.

CYSTS.—Etiology.—Most of the cases reported as pancreatic cysts are really, as Mr. Jordan Lloyd pointed out, encysted collections of fluid in the neighbourhood of the pancreas, and should therefore be spoken of as pseudo-cysts (Körte) or peripancreatic cysts. The majority of these are collections of fluid in the lesser sac of the peritoneum with occlusion of the foramen of Winslow by a low form of peritonitis set up by the presence of the fluid (*vide* also Vol. III. p. 1014). When the collection has formed rapidly, extravasation has probably taken place directly into the sac, whereas in the more slowly forming collections a haemorrhagic pancreatitis may have been the starting-point. The physical signs of such pseudo-cysts do not differ from those presented by true cysts, and it is generally only after operation, and not always even then, that the differential diagnosis can be made. These cases, which are commoner in males than in females, often give a history of injury, which may either set up chronic pancreatitis with secondary peritonitis and the appearance of a tumour after a considerable interval, or if the fluid has rapidly accumulated produce extravasation of blood and pancreatic fluid into the lesser sac of the peritoneum, the contents being therefore much the same as in a true cyst. Dr. Theodore Fisher discussed fully the relation of peritoneal sanguineous cysts to cysts of the pancreas, and brought forward 22 cases. The cases are distributed over all periods of life, from eight years upwards; 14 were males and 7 females. There was a history of injury in 6. When the collection of fluid has reached a certain size it generally becomes stationary, and although vomiting and abdominal pain may cease the patient continues to waste and has a sallow complexion. Return to health, however, has been rapid as soon as the cyst has been drained (*vide* Vol. III. p. 993). It has also been suggested that in some cases the haemorrhage may have come from a suprarenal capsule. Some of these cases have been associated with fat-necrosis, and have therefore been pancreatic in origin. There is very little doubt that whilst some may be associated with damage to the pancreas, others clinically indistinguishable have nothing to do with the pancreas. The fluid may collect in the lesser sac of the peritoneum, between the layers of the mesentery, or behind the mesocolon, and is often due to vascular degeneration.

True retention-cysts may be either single or multiple. The retention of pancreatic secretion may arise from various causes, and be due either to obstruction or to compression of the duct. Chronic pancreatitis is one of the most common factors leading to compression and constriction of the ducts by cicatricial tissue. But occlusion may be the sequel of cicatrisation of a duodenal ulcer, or result from pressure exerted by a large tumour in the neighbourhood. A pancreatic calculus in the duct or a gall-stone in the ampulla of Vater has not infrequently been found. In some cases, however, the cause cannot be determined.

Experimentally Senn found that ligature of the pancreatic ducts in animals caused dilatation only, and not the formation of a true cyst; possibly an intermittent obstruction would be more likely to lead to

the production of one. In most cases there is probably some change in the pancreatic juice itself, and there is no doubt that the extension of infection from the duodenum may lead to obstruction and dilatation of the duct with retention of its contents. Several cases have presented well-marked chronic pancreatitis, which may have been the cause rather than the result. Other associated conditions are tumours, enlarged glands, and in one case obstruction of Wirsung's duct by a *lumbricus* (*Durante*).

Pathology.—Retention-cysts vary considerably. The effect of obstruction of Wirsung's duct in the head may lead to a single large cyst containing many pints of liquid, to fusiform dilatations of the duct, or to multiple cysts of various sizes, sometimes no larger than peas. In chronic cysts the wall is generally smooth, surrounded by dense fibrous tissue, with irregular projections which indicate the remains of other cysts which have fused together; the wall may bear papillary outgrowths, and be lined by cylindrical epithelium. The contents vary very much. The fluid may be turbid, of a dark reddish-brown, yellow, or greenish colour, and in some cases may consist largely of recent or altered blood. Rarely it has been clear, colourless, and limpid. The fluid is generally alkaline, viscid, albuminous, with a specific gravity of 1010 to 1025, and microscopically shews more or less degenerated epithelial cells, leucocytes, cholesterol, and occasionally leucine and tyrosine. Occasionally it is gelatinous, colloid, or purulent. In one case the fluid was acid (Bozeman). The fluid may emulsify fat, change starch into sugar, and digest albumin and fibrin in the same way that pancreatic juice does; the older the cysts the less likely are all these reactions to be present. From the point of view of diagnosis stress is often laid on these characteristics, but other fluids of the body possess amylolytic and emulsifying powers (Boas), whilst the fluid contents of a pancreatic cyst are usually devoid of trypsin. The presence of blood in the cysts has also been regarded as of considerable diagnostic importance. This opinion is based particularly upon the appearance of the fluid from assumed cysts of the pancreas following injury. As has already been stated, such accumulations of fluid, even if they present the properties of pancreatic juice, are not true cysts, but rather encysted collections in the lesser sac into which the pancreatic ducts may have opened. Undoubted pancreatic cysts more often contain no blood, and circumscribed collections of sanguineous fluid in the vicinity of the pancreas may lie wholly outside this gland. Single cysts are larger than the multiple ones, and may contain as much as 14 pints of fluid. Cysts occur more often in the tail than in the head. They are sessile, and are but rarely pedunculated and generally are matted to the tissues in front.

Multilocular Cysts.—Some recorded cases of multiple pancreatic cysts were really retention-cysts, but it has been shewn by Salzer and Hartmann that cystic adenomas may arise from the pancreas; these formations, though extremely rare, are analogous to ovarian cystomas. Fitz in 1900 collected 7, and Cumston in 1903 15 cases of benign multilocular

pancreatic cysts. The walls are lined by columnar epithelium. From a woman aged twenty-five years Dunning removed a cyst, the size of an adult's head, which was so freely movable that it passed below the umbilicus when the patient stood up, and gave rise to difficulty in the operation ; it was diagnosed as a tumour of the left kidney, as there was resonance in front of it. It was a cystadenoma of the pancreas, but there was some doubt as to its origin from the Wolffian body. Occasionally, as in one case recorded by Hartmann, they may be associated with pancreatic carcinoma, the malignant nature being clearly shewn by the occurrence of metastases in other organs.

Congenital cystic disease of the pancreas is very rare, and is of no clinical importance. In one case it was associated with a similar condition in the liver, cerebellum, and kidneys (Pye-Smith). The cysts are minute and multiple, and are not suspected during life.

Hydatid cysts in the pancreas are so rare that the pancreas is not included among the organs affected with hydatids in the 1900 cases collected by Thomas. Dr. Hale White records the case of a boy, aged six, with a large hydatid of the head of the pancreas pressing upon the bile-duct, and leading to dilatation of the bile-ducts and gall-bladder and cirrhosis of the liver. The patient presented all the common symptoms of retention of bile. Briggs also refers to a case of old hydatid in the pancreas shewing sarcomatous infiltration of its walls.

As the pancreatic cyst increases in size it causes atrophy of the gland, the lobules of which are to be found in its wall ; or it may project from the pancreas as a pedunculated tumour. The stomach is usually pushed upwards, more rarely downwards, and the transverse colon lies in front or below. A small cyst may lie to the left or right of the median line according to the part of the pancreas from which it arises. At first the larger cysts usually occupy the epigastric and the left hypochondriac regions, but they may subsequently extend into the right hypochondrium, and the lower border may be found at the brim of the pelvis. The anterior wall of the cyst may be fused with the posterior wall of the stomach, rendering extirpation difficult, if not impossible. The cyst may rupture into the lesser peritoneal sac, the general peritoneal cavity, or the stomach. Rupture into the lesser sac may explain the presence of a large cystic tumour, communicating with the interior of the pancreas in those cases in which a considerable portion of the organ remains unaltered.

Symptoms.—These vary widely in different cases according to the site, causation, and rate at which the cyst has grown. Sometimes there are no definite manifestations before the appearance of a tumour, and usually early symptoms are due to the condition which leads to the formation of the cyst, whereas the later symptoms are due to the presence of the cyst. In cases secondary to pancreatitis there will have been dyspepsia, loss of flesh, and epigastric pain for some considerable time. In other cases which are due to obstruction of the duct, attacks of paroxysmal pain with jaundice, wasting, and vomiting will occur.

According to Mr. Mayo Robson, large, bulky, pale motions, with undigested muscle-fibres and excess of fat accompanied by marked loss of flesh, together with a "pancreatic reaction" in the urine, will generally be found when the disease is due to pancreatitis. Although the cyst usually grows slowly and may remain quiescent for years, even becoming smaller for a while, it may appear soon after an attack of pain and vomiting, and rapidly enlarge within a few months. When haemorrhage takes place from its wall the cyst may attain the size of a child's head within a fortnight. With the appearance of the cyst the patient is liable to attacks of epigastric pain more or less constant and severe, and often lasting for long periods, even months. The pain radiates from the epigastrium to the left shoulder, and may start without obvious reason or with vomiting and diarrhoea, associated with tenderness and fulness. Sometimes there is jaundice and sometimes intestinal haemorrhage. The wasting may be marked or slight. When there is haemorrhage into the cyst the symptoms rapidly become severe, and may necessitate active treatment without delay.

There is usually a smooth rounded tumour presenting first in the left hypochondrium between the costal cartilages and the median line; as it enlarges it causes a swelling of the upper half of the abdomen which, in exceptional cases, may extend from the ensiform cartilage to the pubic symphysis and into both flanks; it is globular, resistant, inelastic, and smooth on the surface. As a rule the cyst is slightly movable, both vertically and laterally, and often transmits pulsation from the aorta, but is not expansile. It is dull on percussion where not covered by the stomach or intestines, and on auscultation a systolic murmur transmitted from the adjacent aorta is sometimes audible. The smaller and more deep-seated the cyst, the more likely is it to suggest a solid tumour; on the other hand, fluctuation may be obtained in a large and superficial cyst. The pressure of the contained fluid may be such that the liquid will spurt several feet from a trocar plunged through the wall. As the tumour becomes more obvious the epigastric pain and digestive disturbances are apt to be more persistent, and the larger its size the greater the loss of flesh and strength. From its size or situation the cyst may interfere with the descent of the diaphragm and so embarrass respiration; it may press upon the portal vein or inferior vena cava and cause ascites or anasarca, or on the intestine and give rise to symptoms of obstruction. In rare instances fat and an excess of undigested muscular fibre have been found in the faeces, and albumin or sugar in the urine.

Diagnosis.—Physical are more important than rational signs in establishing the diagnosis of a cyst of the pancreas. A smooth, rounded tumour, often giving a dull note, is to be recognised, first appearing in the epigastrium or left hypochondrium, slightly movable especially vertically, and usually separated from the liver and spleen by a resonant area. The stomach may be distended by giving tartaric acid and bicarbonate of sodium in separate solutions, and the colon by distending it with air. We can then ascertain their relations. Usually the stomach will be in

front of and often above the tumour, whilst the colon may be below, less often in front of it.

The region of the abdomen in which a cyst may be present will depend upon whether it has originated in the head or the tail, and also on its relation to the mesenteric vessels and the omentum. Usually the cyst is above and slightly to the left of the umbilicus, but it may lie in any region, and may even occupy the whole abdomen. It may therefore be confused with cysts or tumours of the kidneys, spleen, liver or gall-bladder, mesentery, ovary, and the suprarenals, and even with ascites.

Some *retroperitoneal cysts* arise from the remains of the Wolffian body, and may displace the stomach in any direction, and may even push forward the aorta and cava. They are usually thin-walled, of large size; they contain cholesterolin, are freely movable, and can be enucleated. They closely resemble a parovarian cyst, and may be in close relation to the pancreas. They are usually benign, and are unaccompanied by any symptoms beyond those of a mechanical character. Monprofit, who removed one successfully, was compelled to excise the spleen and the tail of the pancreas. He came to the conclusion that it had arisen from the remains of the Wolffian body behind the mesocolon. The diagnosis can but rarely be made before operation, and as the majority recover from operation the deep-seated nature of the mass may preclude accurate determination of its relations and etiology.

Treatment.—It is obvious that medical treatment is of no permanent avail in such cases, but occasionally the question arises whether immediate operation is imperative in some of the acute cases, or whether it is better to delay until the acute process has passed off. It is almost impossible to decide in any particular case whether the increase in size will be steadily progressive or whether there may be a stationary period, but as a rule the steadily progressive nature of the symptoms precludes delay. The risk of opening the abdomen is so much less than it was ten or fifteen years ago that it is much safer to perform a laparotomy than to attempt to drain the cyst by aspiration, which should never be employed even for diagnostic purposes. Incision and drainage of the sac lead to success in a considerable percentage of the cases, and the high mortality attaching to complete extirpation of the cyst renders this procedure inadvisable unless the cyst is pedunculated, or arises in the tail of the pancreas. Usually the cyst is drained from the front, but some have been successfully dealt with from the loin. When the abdomen is opened the relation of the stomach to the cyst should be determined, and the organ may be pushed upwards if necessary. The sac may be emptied by a trocar, the opening enlarged, and a drainage tube inserted, the edge of the cyst being secured to the muscular wall of the abdominal incision or packed round as may be found more desirable. Mr. Mayo Robson and Mr. Cammidge have collected the statistics of 160 published cases of pancreatic cyst, in 138 of which incision and drainage were performed with sixteen deaths, giving a mortality of 11·6 per cent; in 15 cases

excision was performed with three deaths, giving a mortality of 20 per cent, and in 7 partial excision, with one death, a mortality of 14·3 per cent; the deaths occurred within a very few days, in eight of them from peritonitis. They consider that in the more extensive tables collected by others, some of the cases have been counted twice, and that in others the data were insufficient to justify their inclusion in the comparison.

CALCULI are extremely rare, less than 100 cases being on record. Out of 11,000 autopsies at Guy's Hospital there were 3 cases only, all in elderly men; they were multiple, white, irregular in shape and branched; in one case there was a mass resembling white coral, and in another a number of irregular, white, jagged calculi. They are met with most frequently between the ages of thirty-five and fifty-five years. The pancreas in which concretions are found is not normal, probably always shewing catarrh of the ducts, stagnation of the secretion, and the changes due to infection; the ducts are commonly dilated. The pancreas is often atrophied, and there is generally chronic interstitial inflammation. Suppuration is very rare; and although some authors have stated that calculi may be associated with malignant disease of the gland, this must be very exceptional. Concretions may be found in all parts of the duct, but are usually in the head, and only rarely towards the tail. Not infrequently gall-stones have also been found in the biliary passages. Retention of pancreatic secretion alone is not sufficient to produce calculi, for in many cases in which the orifice of the duct is blocked the pancreas is free from calculi, and, on the other hand, when calculi are present the orifice of the duct is not invariably occluded. Moreover, the stones contain a considerable amount of carbonate of lime, which is not present normally in pancreatic secretion. *Bacillus coli* and other organisms have been found in the calculi.

Calcareous deposit may also take place in the tissue and ducts as the result of inflammation; a man, aged sixty-five, had cholecystotomy performed for chronic jaundice with a dilated gall-bladder and an indurated mass in the head of the pancreas; the jaundice disappeared, but he died from pneumonia six months later, and the autopsy disclosed a hard calcareous mass in the head of the pancreas surrounding a cavity and dilatation of Wirsung's duct. There had evidently been some local suppuration. In this case the calcareous deposit was in the tissue rather than as a loose concretion. Usually five to ten calculi are present; in rare instances there is a solitary calculus, but as many as 300 calculi have been found in the pancreas (*Lancereaux*). They vary in size from mere sand to masses an inch and a half in length. They may be smooth or rough, soft or hard, and white, brown, or yellow. Besides carbonate of lime, phosphate of lime, and carbonate of magnesium, they may contain organic protein debris; Mr. Shattock found oxalate of lime in one case. Mr. Mayo Robson has pointed out that the presence of lime renders them markedly opaque to *x*-rays compared to gall-stones, and this may possibly be of diagnostic value in doubtful cases.

Symptoms depend largely on the associated conditions, and are often vague ; in the majority of cases the calculi have been discovered after death. Attacks of colic may be associated with the passage of the concretions, in which case there is epigastric pain running along the left costal margin internal to the nipple line and round to the left scapula, simulating biliary colic but without jaundice, and differing in that the pain is directed to the left. This is often accompanied by vomiting, rigors, and cold sweats. Fragments of calculi may be discovered in the motions. In chronic cases the patients complain of dyspeptic symptoms, the motions are bulky, pale, fatty, and contain an excess of neutral fat, with undigested muscle-fibres ; and in rather less than a quarter of the cases glycosuria has also been present ; the patient also loses flesh and strength. The urine would probably give Cammidge's "C" reaction if there were any associated chronic pancreatitis. Fistulous communications have been known to form with the stomach or duodenum. Mr. Pearce Gould has recorded a case in which a pancreatic calculus pressed on the common bile-duct and caused jaundice.

Treatment.—From the difficulties of diagnosis surgical treatment has been seldom adopted ; according to Oser there are only some 5 cases on record, 3 of which have recovered ; in 1903 Mr. Mayo Robson successfully removed four calculi from a woman aged fifty-seven. Two were removed from the duct by an incision through the duodenum and by incisions into the pancreas itself. Medical treatment can be of little use beyond relieving the pain by sedatives, such as morphine and chloroform, and the local application of heat. Helmitol gr. vii. two or three times a day might help to arrest any infective process in the duct. Holtzmann recommends the injection, three times a week, of 1 c.c. of a 1 per cent solution of pilocarpine for the relief of colic.

TUBERCULOSIS of the pancreas is very rare, occurring in about 1 in 2000 autopsies, and accounting for 1 or 2 per cent of all the cases in which pancreatic disease has been noted. Most of the examples, more particularly those in children, were in generalised tuberculosis. There may be miliary tubercles, small yellow nodules, or occasionally larger caseous masses. For example, at the autopsy on a child aged one year at Guy's Hospital, the head of the pancreas was enlarged and occupied by a soft caseous mass with a ragged-walled cavity in the centre where the tissue had broken down. In some instances caseous lymphatic glands indent the pancreas, and at first sight suggest tuberculosis of that gland. It has been shewn by Carnot (8) and others that it is not easy to produce experimental infection of the pancreas with tuberculosis. Injection of an emulsion of tubercle into the gland generally produced a fibroid pancreatitis.

Tuberculosis of the pancreas is not of any clinical importance as it is usually part of a generalised infection ; but in one or two cases operations have been performed on nodules which have proved to be tuberculous masses situated in the pancreas or in the neighbouring lymphatic glands.

Oser quotes Mayo and Sendler as having met with tumours perceptible by abdominal palpation.

SYPHILIS affects the pancreas in two ways : as a chronic indurative pancreatitis, and as a gumma. Pancreatic lesions are much more frequent in inherited than in acquired syphilis, the organ being affected in 20 per cent of the cases of the inherited disease in new-born infants ; it is thus less often attacked than the liver, spleen, or bones, but more frequently than the thymus, heart, intestines, and kidneys. Out of 23 cases in which the pancreas was affected, syphilitic changes were also found in the liver in 21, spleen 17, in the bones 15, lungs 10, heart and thymus each 5, intestines 4, kidneys 3, and testicles 1. We may therefore conclude that the liver is practically always implicated when the pancreas is, and very probably if the pancreas was always examined microscopically whenever syphilitic changes were found in the liver the organ would be found diseased in a considerable proportion of the cases. Dr. Rolleston has published a case of syphilitic obliteration of the bile-ducts associated with an extreme interstitial pancreatitis. Birch-Hirschfeld (1875) and Schlesinger (1898) shewed that the lesions were less rare than had been supposed (27 out of 124 cases of congenital syphilis). There is a chronic overgrowth of connective tissue with disappearance of the glandular cells, but the islands of Langerhans escape. The organ is increased in size, and becomes hard and grey. Schlesinger believes that the lesions may occur before the later months of fetal life. Miliary gummas have been described (Müller).

In adults syphilitic infection gives rise to chronic pancreatitis much more commonly than to gumma, the organ being indurated, increased in size rather than diminished, and the head more affected than the tail.

The symptoms of syphilitic disease of the pancreas are generally those of a chronic pancreatitis such as dyspepsia, great wasting, marked jaundice with fatty stools, and evidence of syphilis elsewhere. The presence of diabetes in syphilitics would suggest that antisyphilitic treatment should be tried. At the autopsy of a man aged twenty-six who had died with aortic aneurysm and a gumma of the heart, a gummatous mass half an inch by a quarter was found in the pancreas, the adjacent arteries were thickened, and there was well-marked interstitial pancreatitis. Obstructive jaundice due to a gumma in the head of the pancreas was successfully relieved by anastomosis of the gall-bladder with the colon (H. B. Robinson). Oedema of the feet and ascites due to pressure on the inferior vena cava and portal vein have been observed (*vide p. 290*).

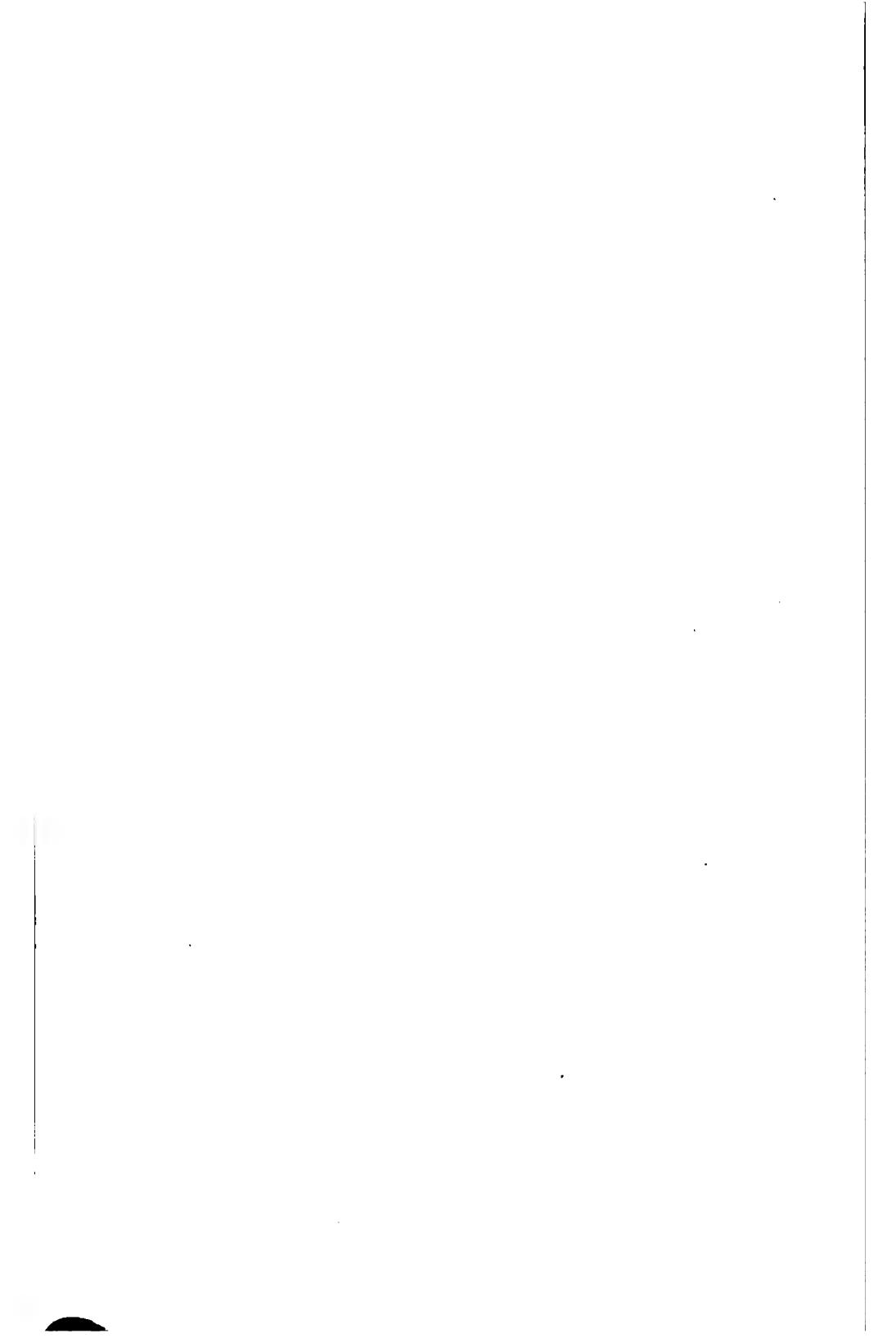
G. NEWTON PITT.

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DISEASES OF THE DUCTLESS GLANDS, AND SOME OTHER CONDITIONS

DISEASES OF THE THYROID GLAND.

INTRODUCTION.

CRETINISM.

MYXOEDEMA.

EXOPHTHALMIC GOITRE.

ACROMEGALY.

DISEASES OF THE ADRENALS.

ADDISON'S DISEASE.

OTHER DISEASES.

DISEASES OF THE SPLEEN.

LYMPHADENOMA.

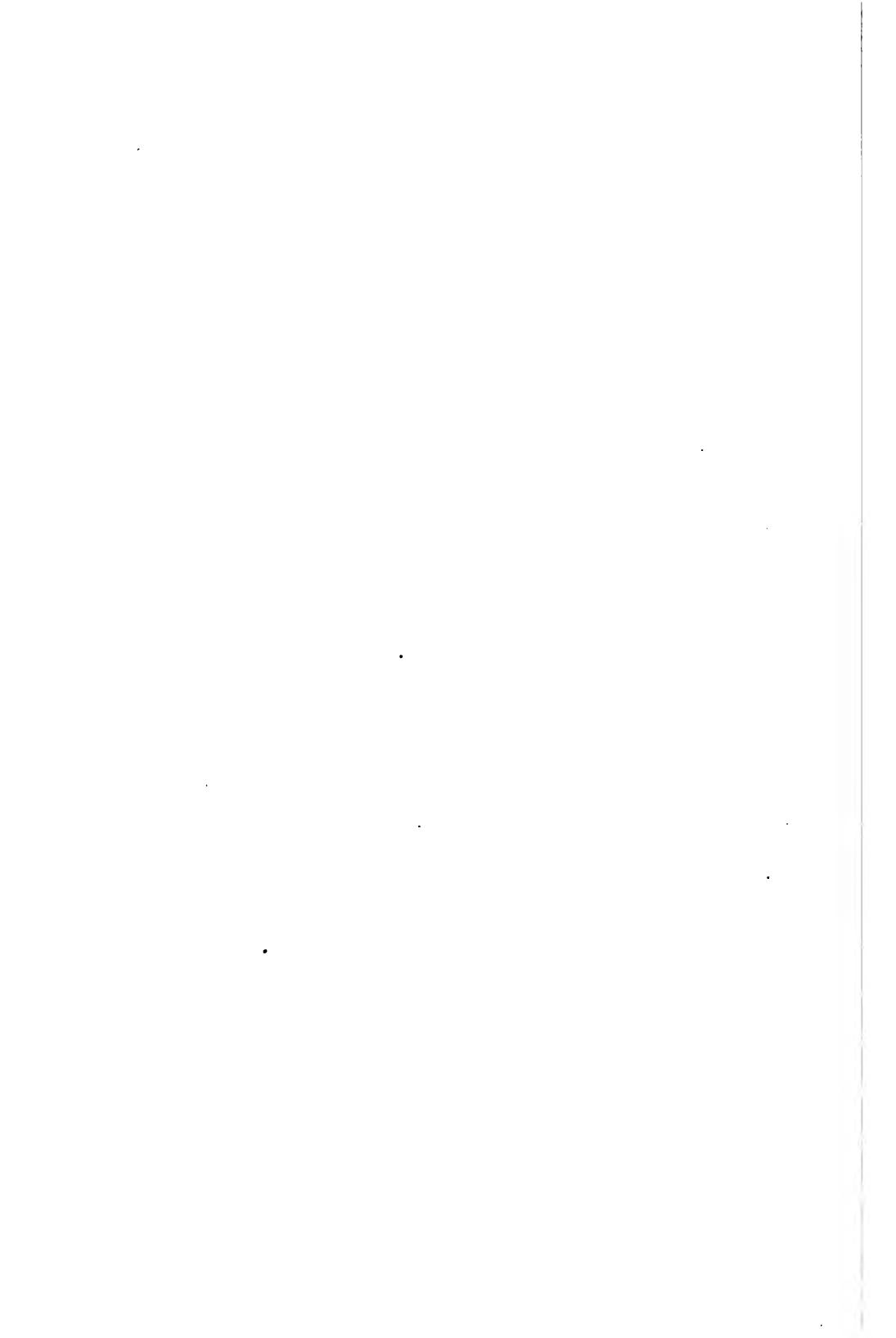
STATUS LYMPHATICUS.

INFANTILISM.

OBESITY.

ADIPOSIS DOLOROSA.

OEDEMA.



DISEASES OF THE THYROID GLAND

INTRODUCTION

By HECTOR MACKENZIE, M.D., F.R.C.P.

Anatomy of the Thyroid Gland.—The form, structure, and anatomical relations of the fully developed thyroid gland are so well known that only those special features which are of importance in connexion with the consideration of its functions need be referred to here. The gland consists of two lateral lobes, of which the right is usually the larger, united by a transverse isthmus. The lobes are in close apposition to the sides of the larynx and trachea. The isthmus varies in breadth from a quarter to three-quarters of an inch, and lies in front of the trachea between the second and fourth rings. The gland is covered with a capsule of dense areolar tissue. It is richly supplied with blood-vessels and lymphatics which, with the nerves, penetrate into and traverse its interior, supported by a network of interstitial tissue. There are two main arteries on each side, the superior and inferior thyroid, which are sometimes supplemented by a third, the thyroidea ima. These arteries are remarkable for their relatively large size and for their tortuosity and their numerous ramifications and anastomoses. The veins which leave the gland are three in number, the superior, middle, and inferior thyroid, the two first joining the internal jugular, the last the innominate. According to Sappey, the veins do not have any valves. The lymphatics run into the superior and inferior deep cervical glands. The nerve supply comes from the middle and inferior cervical ganglia of the sympathetic and from the vagus. Nerve fibres from the descending branch of the hypoglossal have also been described.

Histology.—The gland substance consists of an aggregation of closed vesicles, rounded or polyhedral in shape, supported and divided into imperfect lobules by a connective-tissue network continuous with the fibrous capsule. The vesicles are of varying size, the largest having a diameter of about 1 mm.; their walls are formed of hyaline material and a single layer of cubical or columnar epithelial cells without any basement membrane. They are filled with a yellowish glairy fluid, the so-called colloid material. With this there may be mingled detached

epithelial cells together with a few leucocytes and erythrocytes undergoing disintegration and decolorisation. In the periphery of the colloid, vacuoles are sometimes to be seen. Two varieties of epithelial cells have been distinguished which, after Langendorff, have been termed the principal cells (*Hauptzellen*) and the colloid cells. The colloid cells are the cells which are more or less distended with the granular matter which forms the secretion. The granules are readily stained in the same way as the colloid material, and these cells may be said to be more oxyphil than the principal cells. The latter stain but slightly. The nucleus of the cells is round and large, and stains more deeply in the case of the colloid types; the colloid cells are the larger. The two kinds of cells are different stages only, the resting and the discharged state of the secreting cells of the glands. The capillaries contained in the connective tissue are brought into the closest contact with the epithelium, and sometimes may be seen projecting between the cells. Glandular cells are also found outside the vesicles either singly or in groups or clumps. They are polyhedral, and shew similar changes of state to those of the epithelium of the vesicles due to the varying amounts of granular matter they contain. According to Dr. Forsyth they are most abundant in the thyroid in infancy, and are less common in later life.

Weight.—The weight of the glands varies during childhood between 90 and 180 grains, and in adults between 1 and 2 ounces. In infants of a few days old I have found the weight of the gland to vary between 15 and 30 grains. According to my observations and to those of Sir Stephen Mackenzie, the weight of the glands is usually proportional to the weight of the body irrespective of the age of the subject. The statement made on the authority of Huschke as long ago as 1844, that in the fetus and during early infancy the thyroid gland is relatively much larger than in after-life, is not borne out by these observations. It is generally stated in textbooks that the weight of the gland is greater in females than in males, but Weibgen's observations give an average weight of 528 grains for men and 450 grains for women.

Development.—The first traces of the thyroid gland in the embryo are three diverticula, two lateral and one median, which are formed from the hypoblast lining the primitive pharynx. The median diverticulum is developed at the level of the second visceral arches, the lateral at that of the fourth visceral cleft. The former for a time continues as a hollow sac which communicates with the pharynx through a narrow neck, the thyreo-glossal duct. Subsequently the sac is obliterated and the duct closes, the position of its external opening being indicated by the foramen caecum on the dorsum of the tongue. The lateral and the median segments subsequently fuse together to form the complete gland in front and at the sides of the upper part of the trachea and larynx. At first the gland consists of a mass of polyhedral cells, which later on are grouped into clumps by the ingrowth of connective tissue. As early as the sixth week the cells of the human thyroid are arranged so as to form the walls of small vesicles. The proportion of epithelial cells to inter-

stitial cells gradually becomes greater until the adult arrangement of cells is reached. The cells gradually assume the staining reactions of the colloid cells, and small granules make their appearance in them, whilst drops of colloid fill the interiors of the newly formed vesicles.

In some animals low in the scale and in fishes there is persistence of the communication with the pharynx. According to Andriezen this is the case in the amphioxus, ascidians, and lower vertebrata. In the amphioxus the thyroid body is a hypobranchial organ; in ascidians it is a mass of glandular tissue, the endostyle organ. In fishes, although embedded in the tissues, the gland has an opening into the pharynx. In these animals, therefore, the secretion enters the body by way of the pharyngeal tract. Andriezen suggested that, passing with the currents of water over the vascular arches, the secretion is there absorbed, enabling the respiratory organs to take up oxygen and carry on the gaseous metabolism more readily. Thus the organs may be looked on as associated anatomically with a primitive respiratory system, and physiologically with the respiratory gaseous exchange. According to Sir V. Horsley, the epithelial cells of the human thyroid gland shew signs of functional activity from the sixth to the eighth month of fetal life. It is not until old age that retrogressive changes necessarily appear. Then the interstitial fibrous tissue increases, the epithelial cells degenerate, and their remains are shed into the shrunken vesicles which contain but little colloid.

Accessory Thyroids.—Thyroid tissue is not strictly confined to the limits of the thyroid gland. Small extraneous masses of thyroid tissue or accessory glands are frequently present. The most usual situations for these are the region of the hyoid bone, the region of the thyroid gland, where they occur under or behind the lateral lobes, and the region of the aorta and great vessels.

The Parathyroid Bodies.—Either embedded in the thyroid substance or lying external to it are to be found certain small bodies, which, whilst superficially resembling thyroid tissue, are found to present important structural differences from it. These bodies have been called parathyroids, and were first described in man by Sandström in 1880, although they had been noticed by Owen in the rhinoceros in 1862. These bodies have in recent years been brought into great prominence, and have been considered of even greater vital importance than the thyroid body. Their intimate connexion with the thyroid body has greatly complicated experimental research as to the functions of the latter, in consequence of the difficulty of removing one without the other.

There is considerable variation in the number and position of the parathyroid glands in man as well as in the lower animals. Commonly in man they are attached to the thyroid gland, and are four in number, but, as will be seen, this is by no means constant. Whilst there is the greatest diversity in their position, the lower gland usually lies near the posterior edge of the thyroid gland in the loose tissue among the branches of the inferior thyroid artery, and the upper gland usually at the posterior

edge of the thyroid gland close to the oesophagus. Welsh gives the position of the upper gland as the posterior wall of the oesophagus or pharynx at or near the junction of the two and quite separate from the thyroid tissue. That of the lower gland is more variable, and is either close to the lower edge of the lobe or immediately or some distance below it.

Dr. Forsyth, who made an exhaustive examination of 66 human subjects, found that in somewhat less than half four parathyroids were present; in a third of the cases more than two parathyroids were present on one side, the number varying from three to seven. In seven of the subjects there was not more than one. The position of the upper gland only is at all constant. It is, however, exceptional for the glands to be situated at any considerable distance from the thyroid lobes, and Dr. Forsyth found them invariably in the same compartment of the deep cervical fascia. No parathyroid was found at any distance superior to the thyroid. It is noteworthy that their most common position is also that of accessory thyroids, with which they may be blended. They have also been found connected with the thymus. The average glands are from 6 to 8 mm. in length, 3 mm. in width, and 1 or 2 mm. in thickness. They are flattened and ovoid in shape, and soft, flabby, and inelastic in consistency. They are usually of a pale pink colour, and have a smooth glistening surface over which a few vessels ramify.

The parathyroid has a thin capsule of connective tissue from which fibrous trabeculae are given off, and permeate the gland so that it is divided into small polyhedral sections. As in the case of the thyroid body the fibrous tissue carries with it a lavish supply of blood-vessels and lymphatics. The cells are grouped irregularly in clumps lying in the meshes of the fibrous stroma. The cells are polyhedral and contain a single nucleus. Two kinds of cells have been distinguished, resembling those of the thyroid. These are, first, cells which contain much protoplasm and are eosinophil or oxyphil, having a decided affinity for acid dyes, and which are analogous to the "colloid cells," and, secondly, cells which appear clear and take little if any stain, the "principal cells." The former are the resting cells or cells accumulating secretion, the latter the fatigued cells, or cells which have delivered themselves of their secretion. Cells may be found at various stages between rest and fatigue. Minute droplets of secretion may be observed lying in the midst of the cells, which are sometimes grouped around it so as to give rise to the appearance of a vesicle. According to Dr. Forsyth, the secretion of the parathyroid cells is identical with the thyroid colloid in appearance and staining reactions.

The appearance of the parathyroid bodies at or shortly after birth presents certain peculiarities. The connective-tissue stroma is more distinct. The cells fill its meshes, but appear to be in the inactive stage, scarcely staining with acid dyes. It is not until about the third or fourth year, or even later, that the cells shew signs of commencing activity.

The Colloid Substance.—The characteristic yellow glairy fluid, the so-called colloid substance, is the secretion of the thyroid gland, and many investigations have been made with the object of determining its exact nature and chemical composition. Baumann first shewed that iodine is a constant constituent of the colloid, being found in organic combination principally in the form of a protein molecule, the iodine-containing thyreo-globulin of Oswald. The colloid matter can be obtained in a state of purity according to the method of Dr. R. Hutchison, from a dilute alkaline extract of the fresh glands by precipitation with acetic acid, reprecipitation, and washing with alcohol and ether. Thus obtained it is a very light brown, tasteless, and odourless powder. Usually thyroid substance will yield one-tenth of its weight of colloid substance. Two views have been held as to the origin of the colloid substance; the first was that it was the unaltered secretion of the epithelial cells; the other that it was the result of a degenerative change in the cells, which were then shed into the interior of the vesicles. The first view is supported by the existence of transitional cells intermediate between the "principal" and the "colloid cells"; the cell in the resting stage gradually accumulates secretion, of which it then delivers itself, and is transformed into a discharged cell or cell in the stage of fatigue. No doubt some of the colloid cells are shed, but the secretion is only to a small extent composed of these. The colloid substance not only fills the vesicles but also the lymph-spaces in the interstitial tissue, and its presence can be demonstrated in the lymphatic vessels coming from the gland; this was first shewn in 1835 by King, who caused the secretion to flow into the lymphatics by gentle pressure on the lobes of the gland.

The colloid substance is compound, and can be readily split up by gastric digestion into a protein and a non-protein part. The protein constituent, which forms nearly half of the substance, consists of albumoses, and is a colourless hygroscopic powder with a bitter taste. The non-protein body is a dark brown, odourless, and tasteless powder. Both these constituents appear to possess the physiological properties of the colloid matter, but the non-protein in a considerably higher degree than the protein. The non-protein part appears to be almost, if not quite, identical with the thyro-iodine of Baumann obtained by boiling the gland with dilute hydrochloric acid, separating by filtration the precipitate which falls, and purifying the latter by further treatment. Other bodies not containing iodine have been separated from the gland, but none of these possess the specific action of the colloid substance; among these may be mentioned a nucleo-albumin, extractives, creatine, xanthine, a body called thyreo-antitoxin by Fraenkel, Drechsel's basic products, and Oswald's iodine-free thyreo-globulin. The activity of a preparation of thyroid gland appears to be proportional to the amount of iodine it contains, and only iodine-containing products possess any activity. No artificial preparation of iodine has so far been found to possess the same property.

Iodine and other Constituents of the Colloid.—Iodine thus appears to be

a peculiarly essential element for the function of the thyroid gland. The normal gland contains from '03 to '09 per cent of iodine, the proportion varying under different conditions of life. The colloid substance contains from '3 to '9 per cent of iodine. The amount of iodine in the whole gland varies between 2 and 9 milligrams. Iodine is not found in the thyroid gland of the fetus or the newly-born, and it is not until one year after birth that it can be detected. After this age the relative amount of iodine remains fairly constant until old age, when it declines. During pregnancy the iodine content has been found to be considerably lessened. Goitres, whilst containing a small percentage of iodine, may shew a very considerable increase in the total amount present, except in the case of purely parenchymatous or fibrous goitres. In parenchymatous, including exophthalmic, goitre, the iodine content may be as low as '0002 per cent. That in the case of the exophthalmic variety this may only be the consequence of the rapid re-absorption of the secretion is shewn by those cases in which the vesicles are filled with colloid material. A. Kocher found as much as 40 to 50 milligrams in one lobe of the gland in a case of this kind. Fibrous goitres, or parts which have undergone cystic degeneration, often contain no iodine. Among the lower animals, the proportion of iodine is highest in herbivora, lowest in carnivora, in which it may be nil. According to Mendel the amount of iodine present in the human parathyroids is both absolutely and relatively greater than in the thyroid.

Phosphorus is a constant constituent of the colloid substance, but the proportion is considerably lower than that of iodine. Arsenic has also been detected by Gautier and Bertrand.

The Functions of the Thyroid Gland.—Before the last quarter of the nineteenth century there was little if any real or certain knowledge on this important subject. Of the numerous hypotheses framed to account for the presence of the thyroid, some few shewed a glimmering perception of the truth, but most of them, if ingenious, were fanciful and far-fetched. The history of this subject has been comprehensively summarised by Sir Victor Horsley. Strange as it may seem, the gland was regarded as absolutely functionless by a number of eminent scientific men during the last century. Some surmised that the gland was seated in the neck simply to give a shapely roundness to its contour ; some looked on it as providing a protective covering to the numerous important vessels and nerves underlying it ; others thought that it had important relations with the larynx, which it helped to support, and that it was in some way connected with the quality of the voice. Others, again, impressed by the number, size, and meanderings of its blood-vessels, concluded that it acted as a kind of safety-valve regulating the blood-supply of the brain. Another suggestion was made that each lobe had a special nutritive relation to the corresponding cerebral hemisphere, manufacturing some substance needed by the brain. Another hypothesis was that the gland swelled during sleep, over which condition it exercised some control. It was alleged by others that there was a close relation between the thyroid gland and the female sexual organs, in support of which was urged the

variation in size at the menstrual periods or under the influence of strong sexual excitement, and the greater frequency of thyroid disorders in the female sex. Others, again, supposed that the gland had special relations with the emotional nervous system, swelling or shrinking under such influences as anger, joy, or sorrow. The more rational hypotheses were those which regarded the gland as the producer of some substance of use in the bodily economy. It was thus considered to be :—(1) A direct blood-forming organ ; (2) an indirect blood-forming organ ; (3) an organ which modified or destroyed substances circulating in the blood and harmful to the body ; (4) an organ which secreted some substance necessary to the body for the processes of metabolism.

Our present knowledge of the function of the thyroid gland has been obtained in several different ways, namely, by study (a) of the effects, immediate and remote, of experimental removal of the gland in various animals ; (b) of the effects of complete removal of the gland in human beings, usually on account of goitre ; (c) of the symptoms of cretinism and myxoedema, in which the gland is absent or atrophied ; and (d) lastly, of the effects of the internal administration of thyroid substance in healthy conditions as well as when the gland is absent or functionally deficient. The functional importance of the glands was conclusively proved when the remarkable bodily changes present in cases in which the gland was absent or defective were found to disappear under the influence of thyroid feeding. The train of symptoms presented by cases with atrophied thyroid glands was observed to follow complete thyroidectomy, and to be obviated by thyroid feeding. That the functional importance of the gland is greatest in early life is shewn by the more profound alteration in the body which is associated with the absence of function of the gland at that period, and by the much more serious results of experimental thyroidectomy in young animals. Where a gland is of importance to the body, the removal of part of it has been observed to be followed by hypertrophy of the remainder. It was shewn by Wagner that this happens in the case of the thyroid, for when one lobe was removed the other hypertrophied. This result, however, was soon found not to be constant, but to occur in young animals only, another proof of the greater functional importance of the gland in the young. It has also been observed that after complete thyroidectomy accessory glands sometimes hypertrophy. Conclusive evidence of the great physiological importance of the thyroid gland was first given in 1857 by Schiff's observations that the removal of the thyroid gland in dogs and cats was almost invariably followed by profound illness and death. These results, however, passed unnoticed until Schiff repeated his experiments in 1883, after Kocher and Reverdin reported the serious and sometimes fatal results of complete thyroidectomy in the human subject.

It was subsequently found that some animals, such as rabbits, bore the removal of the thyroid well ; and that sheep and monkeys, although profoundly affected at first, might survive the operation for

a considerable time. In some of these animals it was found that accessory thyroids or parathyroids had been left. In the rabbit the external parathyroids are situated on each side of the trachea below and quite apart from the thyroid gland. Hence when the thyroids are removed in these animals, these parathyroids are almost invariably left behind. In the dog, on the other hand, the parathyroids are closely connected with the thyroid, and, as a rule, are removed along with it. From these observations it was concluded that the parathyroids were of vital importance, and that their removal was probably the cause of the rapidly fatal result which followed thyroidectomy in dogs, and sometimes in other animals. An attempt was therefore made to observe separately the effects of removing first the thyroid, and secondly the parathyroids. Accordingly Vassale and Generali extirpated the then recognised four parathyroid glands in ten cats and nine dogs. Nine of the cats and all the dogs succumbed within ten days, the dogs dying more quickly than the cats. One cat survived six weeks, but was then in a state of cachexia. The removal of two parathyroids, or even of three, appeared to produce only transitory symptoms; but the subsequent removal of the remaining one or two resulted in acute symptoms and death. Apparently the internal and external parathyroids were of equal importance, for it made no difference which were removed first.

The experiments carried out by Mr. Edmunds, both before and after Vassale and Generali's work, seemed thoroughly in accordance with their results. He found that if the whole of one lobe of the thyroid of the dog, including the parathyroids, and also the greater part (two-thirds or more) of the other lobe be removed, the animal will live or die according as the parathyroid is or is not left. In the animals which survived, the removal of the remaining parathyroid at a later period, in some cases at an interval of six months after the first operation, was quickly followed by acute illness and death. The acute symptoms due to removal of all the parathyroids in cats and dogs were as follows:—The animal became dull and apathetic, and shewed signs of general muscular weakness. Its gait appeared to be unsteady. Tremors and fibrillar twitchings, together with trismus and rigidity of the posterior limbs, shewed themselves, and there were attacks of dyspnoea. The appetite might be increased at first, but was soon lost. Vomiting, palpitation, scantiness of urine, and sometimes albuminuria, were also observed. Slight convulsions occurred just before death. The symptoms observed in the dog on complete removal of the thyroid gland agreed with these in every respect; except that convulsions came on earlier and were more severe than when the parathyroids alone were removed. In many instances conjunctivitis and keratitis occurred. Two other important symptoms remain to be mentioned; namely, a fall of the body temperature and anaemia. After a preliminary rise, the temperature gradually fell and remained subnormal till death. Leucocytosis and a considerable diminution in the number of the red corpuscles were observed. There was also increased venosity of the blood. The red

corpuscles seemed to have a diminished capacity for taking up oxygen. The effects of removal of the thyroid gland, leaving behind the parathyroids, were studied in dogs. When the animal recovered from the immediate effects of the operation it exhibited no signs of illness. In these cases a small portion of the thyroid had generally been left in addition to one or more parathyroids. The effects of total extirpation of the thyroid gland in monkeys have been carefully studied by Sir V. Horsley, Munk, Edmunds, and others. Two classes of symptoms were observed in them, the acute and the chronic. The acute symptoms closely resembled those observed in the dog. They appeared within a few days after the operation. These symptoms were summarised by Sir Victor Horsley as follows: "*Motion*, tremor, clonic spasm (paroxysmal), contracture, paresis, paralysis. *Sensation*, paraesthesia, then anaesthesia. *Reflexes* gradually diminished. Mental operations normal at first, are soon diminished in activity, and then follow apathy, lethargy, coma." With these symptoms were associated subnormal temperature after an initial elevation, gradual anorexia after voracity, anaemia, leucocytosis, fall of blood-pressure, failure of nutrition with mucoid degeneration of the connective tissues, and usually atrophy and falling out of the hair. The eyelids became puffy with elastic oedema, the features grew heavy and coarse, the skin being rough in some cases, and the hair falling out. The duration of life averaged about twenty-four days.

The chronic symptoms closely resembled those of myxoedema. They were observed in monkeys kept in a comparatively warm temperature. The first few weeks after the operation were characterised by slight attacks of tremor and malaise. Then followed dulness of intellect, diminution of energy, and apathy alternating with idiotic activity. Persistent paresis and an attitude exactly resembling that of a human idiot or cretin were very interesting features. Although the animal fed voraciously it steadily emaciated. The hair fell out in quantity. The voice gradually altered until it became a hoarse croak. The scene was finally closed by coma.

Since 1892 the whole problem of the functions of the thyroid gland has been greatly complicated by the attempts already mentioned to determine the functions of the parathyroid bodies. Gley and his followers concluded from their experimental work that these bodies possessed a function essential to life, and that their complete removal was followed by the death of the animal. According to Dr. Forsyth, however, most of the evidence on which this conclusion is based is open to grave doubt. Moreover, from their experimental work, Vincent and Jolly have recently come to the conclusion that complete parathyroidectomy is, except in very favourable cases, impossible; and with this opinion Dr. Forsyth is in complete accord. Vincent and Jolly consider neither the thyroid nor the parathyroids as essential to life. With regard to Sandström's original view that the parathyroids are merely embryonic "rests," Dr. Forsyth says it is supported by certain facts, but is not definitely proved. Against their embryonic nature he points out that

there are definite signs of activity in the cells. He considers that they are portions of the thyroid gland which have assumed activity but have not formed vesicles, that their tissue may develop into thyroid tissue, that their secretion is indistinguishable from that of the thyroid, and that they are essentially thyroïdal in function. Although it has not been proved that parathyroid tissue can be transformed into thyroid tissue, there is some reason to think that this is possible ; thus the parathyroids are more numerous in infancy, whilst the accessory thyroids are more numerous in adult life.

The results which follow the loss of the thyroid secretion in the human adult can be studied in the condition known as cachexia strumipriva, which ensues after complete thyroidectomy, and in myxoedema, due to atrophy of the gland (*vide p. 345*). The importance of the thyroid gland for the growth and development of the young animal and the human child is shewn by the results which follow its removal, absence, atrophy, or degeneration (*vide art. "Cretinism," p. 334*). The prevention of these consequences, or a return to the normal condition, by administration of thyroid substance, provided it is given sufficiently early, shews what a powerful influence the thyroid secretion exerts during the period of growth. Various experiments made on young animals prove that removal of the thyroid arrests skeletal growth, but, as has been pointed out, the risks from the operation are greatest in early life.

The thyroid secretion in some way exerts a profound influence on metabolism. Where the thyroid function is active there is a decided increase in the tissue changes ; where it is slight, or in abeyance, the tissue changes are correspondingly diminished. The tissue changes have been carefully studied in myxoedema. In that condition the gaseous exchanges are lessened. The oxygen consumption may fall to 50 or 60 per cent of the normal, a lower degree than is observed in any other chronic disease. In spite of taking little food, the patient still puts on flesh. There is also a low nitrogen excretion, amounting to less than 8 or 9 grams daily. If the food intake be increased, nitrogen is readily stored up in the body. The amount of the urine is also below the average. When the myxoedematous patient is treated with thyroid substance, the oxygen consumption soon increases, so that it not only may reach the normal, but exceed it. At the same time the nitrogen excretion increases to twice, thrice, or even four times the former amount, the patient being kept strictly on the same diet. The quantity of urine and the chlorine excretion also increase. At first a part of the excreted nitrogen is derived from the tissues. As is observed in some thyroidectomised animals, the blood is often impoverished in myxoedema, the haemoglobin being diminished to a greater degree than the number of erythrocytes ; with treatment the blood returns to the normal.

When thyroid substance is administered to the non-myxoedematous, the nitrogenous metabolism is frequently altered, the excretion of nitrogen possibly increasing by several grams a day ; but as compared with the case of the myxoedematous subject, the relative nitrogen losses are both

smaller in amount and shorter in duration. The increase in protein metabolism was found by Vermehren to be greater in elderly subjects than in the young, but the reverse is stated by Pfeiffer and Scholz. The change in protein metabolism produced by thyroid feeding is to a great extent independent of diet. Temporary increases in the excretion of chlorides, of sulphur, and of phosphorus, the latter being sometimes considerable, have been observed in some cases. Increased tissue changes may be produced in obese persons by the administration of thyroid substance; but how far this may be the result of increased amount of exercise taken is uncertain.

The effects of increased functional activity of the thyroid gland may be studied in the subjects of Graves' disease. In this disease the total metabolism has been found to be decidedly increased, according to the investigations of F. Müller and others. Magnus-Levy and others have shewn that the minimal metabolism is also increased. In severe cases the former found that the oxygen consumption was much above normal, to the extent of 50 or even 70 per cent. When the acute symptoms subside, and weight is being gained instead of lost, the oxygen consumption diminishes and may fall below normal, the excretion of carbon dioxide also being lessened. If, on the other hand, the disease becomes worse, both the oxygen consumption and the carbon dioxide excretion are still further increased. In order to maintain equilibrium of protein metabolism in Graves' disease, it has been found necessary not only greatly to increase the amount of food generally, but that of protein in particular. Matthes found that 16 to 22 grams of nitrogen had to be given daily before nitrogenous metabolism was maintained. This is the equivalent of 39 to 50 calories per kilogram. This excessive nitrogen metabolism, however, is peculiar to the acute stage, and is not observed in the more chronic forms. Another point of interest in connexion with Graves' disease is that in that malady phosphorus excretion has been found by Scholz to be strikingly increased on the administration of thyroid substance, this increased excretion taking place almost entirely by the bowel. Roos and others have observed an augmented excretion of phosphoric acid both by the urine and faeces in animals fed with thyroid preparations.

The carbohydrate metabolism is influenced to some extent by the thyroid secretion; sugar is excreted in the urine of dogs after thyroid feeding, when large quantities of carbohydrates have been given; and the amount of glucose which can be given without causing glycosuria is less than the average in patients suffering from Graves' disease or in persons who have been treated with large doses of thyroid substance. It appears, on the other hand, that in myxoedema a greater amount of glucose than normal can be retained.

The important connexions of the thyroid gland with the processes of metabolism have prompted some experiments as to the influence of abnormal feeding on the gland. Dr. Chalmers Watson fed fowls entirely on meat for periods ranging from four to sixteen months, and reported

that he had found, when the fowls were subsequently killed, a hypertrophied condition of the thyroid gland. His experiments, however, have been repeated with negative results by Dr. Forsyth, who also examined the thyroid glands of vultures and other birds of prey which feed entirely on meat, and has found in them no indication of increased thyroidal activity, or in fact any peculiarities of microscopical structure or macroscopical appearance.

There has been a good deal of speculation as to the mode of action of the thyroid gland. Two hypotheses only—the “secretion” and the “neutralisation” hypotheses—need be mentioned. The secretion hypothesis has obtained most support, and it is difficult to understand how any other conception can reasonably be entertained. The gland secretes the colloid material, which passes into the lymph stream, and thence into the circulation; there it exerts its effect on the blood and the tissues generally. When the gland is absent, the colloid secretion administered by the mouth enters the circulation, after digestion in the stomach and intestines. What part the secretion plays in modifying the blood is uncertain; it has been assumed that it serves to neutralise some poison formed in the body, possibly as the result of metabolic processes. But the secretion itself is toxic when produced or administered in excess. When given in excess the train of symptoms characterising Graves' disease results. Thus we have one toxin antagonistic to and neutralising another. The neutralisation hypothesis differs from the secretion hypothesis in the assumption that the action of the gland is exerted locally in the gland. It is assumed that, as the lymph passes through the gland, toxic substances are there taken up, and enter into combination with the iodine of the gland. The iodine subsequently reunites with the albumin of the gland, and thus never passes out of it. As Magnus-Levy has pointed out, the iodine substance which possesses the specific action is stored up, not in the cells, but in the colloid contained in the vesicles; and the toxin brought to the gland by the lymphatics would have to diffuse into this colloid, and there undergo a chemical process of neutralisation.

In conclusion, a brief reference may be made to the relations of the pituitary gland to the thyroid and parathyroid glands. In cases of disease of the thyroid, changes in the parathyroids have occasionally been observed. Both in myxoedema and in cretinism, hypertrophy of the pituitary gland has been observed. The structure of the anterior part of the pituitary body very closely resembles that of the parathyroid body. In both glands the clear and the granule cells, the principal and the oxyphil cells, are met with, as well as intermediate cells; and in both, at intervals, drops of colloid may be observed. It is possible, therefore, that, like the parathyroids, the pituitary may take on some of the functions of the thyroid when the latter fails in the discharge of its duties.

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CRETINISM

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SYNONYMS.—*Cretinoid Idiocy*; *Infantile Myxoedema*; *Cretinismus*; *Crétinisme*; *Pachydermie Crétinoïde*; *Cachexia Pachydermica*.

Definition.—A chronic disease arising in early childhood due to absence or deficiency of the normal secretion of the thyroid gland and characterised by imperfect development of body and mind, so that cases left untreated shew stunted growth, with gross deformity of body, changes in the skin, and imbecility. The thyroid gland is either congenitally absent or imperfectly developed, or is affected by fibrosis and atrophy of the secreting structure.

Etiology.—Cretinism has been observed both in an endemic and a sporadic form, and although separate descriptions of these have sometimes been given they are essentially the same. The endemic form is met with in certain particular districts, especially in the valleys of Central Switzerland, Savoy, and Piedmont, and also in those of the

Tyrol, Auvergne, the Apennines, and Pyrenees, and amidst some of the dales in the north of England. It is by no means confined to Europe, occurring also in various parts of Asia, Africa, North and South America, and Australia. Wherever goitre is prevalent, there endemic cretinism will be found. The causes of endemic cretinism are the same as those of endemic goitre, and of the latter the most potent cause is the water used for drinking purposes. It has been found that when a new family comes into a goitrous district goitre appears in the first generation, cretinism in the second or third. Numerous well-authenticated examples of the influence of water in producing the disease might be mentioned. Saint-Lager relates that in Antigagno (Asti) there were three wells, of which two in different degrees were harmful, whilst the third was innocuous. Among the families supplied by the first well there were numerous cases of goitre and cretinism. Those who drank the water of the second well were affected with goitre, but not with cretinism. Neither goitre nor cretinism occurred among those families supplied by the third well. The Sardinian Commission found that in the parish of Bozel in the Tarantaise (Savoy), there were in the year 1848 among 1472 inhabitants 900 goitrous and 109 cretins, whilst in the neighbouring parish of St. Bor cretinism was unknown, although the conditions of life, except for the water-supply, were in every respect similar. The effect of a new water-supply for Bozel from the adjoining hill of St. Bor was that goitre and cretinism so greatly diminished that, in 1864, the French Commission found only 39 cases of goitre and 59 of cretinism remaining. The nature of the specific constituent of water which produces goitre and leads to cretinism is still unknown.

The causation of the sporadic form of cretinism is much more obscure. Some cases have been ascribed to consanguinity between the parents; in others there has been a family history of alcoholism, or of tuberculous or syphilitic disease. Others, again, have been attributed to mental shock, depression, or worry experienced by the mother during pregnancy. There is sometimes a family history of "deformities." In some of the cases I have seen there have been cases of goitre or myxoedema among near relations. But in the majority of the cases recorded there is nothing to explain the origin of the disease, the subjects of which are not uncommonly members of large and otherwise healthy families.

Age.—The disease may manifest itself soon after birth. In rare instances the child is still-born with the cretinoid condition already developed. More commonly it is not until the child is between one and two years old that its abnormal condition is recognised. In other cases it is not until later—between the ages of four and eight, or possibly not until the period of puberty—that cretinoid changes appear, and the child's development is arrested. To the latter cases the name juvenile myxoedema is specially appropriate.

Sex.—The cases under my own observation have been about equally distributed between the two sexes, but that the disease is more frequent

among female than among male children is evident from the collation of recorded cases. In a series of about 110 cases collected by Dr. Rushton Parker, about 60 per cent were females; out of Dr. Fletcher Beach's 114 collected cases, 71 were females; of Professor Osler's 58 cases, 35 were females; of Dr. Byrom Bramwell's 44 cases, 30 were females; of Langdon Down's 11 cases, 8 were females; and of Prof. George Murray's 45 cases, 28 were females. Out of 292 cases, 172 were females, or very nearly 60 per cent. The proportion of three females to two males is therefore approximately true.

Morbid Anatomy.—*Thyroid Gland.*—The essential point in the morbid anatomy of cretinism is the absence or abnormal condition of the thyroid gland. In different cases it is absent, atrophied, or the seat of goitrous enlargement.

(1) In sporadic cases most commonly no trace of the gland can be found. Absence of the gland was first noted by Curling in 1850 in his classical paper on "Two Cases of Absence of the Thyroid Body connected with Defective Cerebral Development." Since then absence of the gland has been found to be the rule in fatal cases.

(2) Atrophy of the gland is much less common, but is found in a small proportion of the fatal cases. In a case recorded by Packard and Hand the alveoli were marked off by bands of white fibrous tissue, most abundant round the larger blood-vessels, which were the seat of calcareous infiltration. The acini were small, and either contained no colloid or traces only. Atrophy and fibrosis was also present in one of Professor Osler's cases; most of the alveoli were almost solid; only a very few were filled with colloid. In some cases the vesicles were filled up by papillary projections and proliferated and desquamated cells. The cells lining the vesicles were themselves much altered.

(3) The presence of a goitre is rare in sporadic cretinism, but is common in the endemic variety. In about 60 per cent of the latter there is a goitre which may be of considerable size. In these cases the changes in the secreting tissue are essentially of the same nature as in those with atrophy. There is increase in connective tissue and diminution of the vesicles, with absence of colloid in most of them.

Other Glands.—Hypertrophy of the pituitary body, which is probably compensatory, has been recorded in a few instances. The thymus has been found to be considerably enlarged in some cases.

The Skeleton.—The most characteristic feature of the skeleton is its arrested growth, and this is most conspicuous in the long bones, which, with the exception of the clavicles, are short, thick, and, when exposed to pressure, deformed. The ends of the bones are often cupped, and there is a superficial resemblance to rickets, but instead of the excessive formation of cartilage at the epiphyses with increase and crowding together of the cells, there is actual arrest of growth. In the endemic form of cretinism the skull is usually brachycephalic, but in the sporadic form it is not uncommonly dolichocephalic. The cranial bones are thickened, and the diploe is diminished. Premature ossification of the

spheno-occipital suture was first described by Virchow, who attached much importance to it and regarded it as causally related to the arrested development of the brain; but it is not a constant feature, the bones having been found ununited in a number of cases, and in one of these as late as the twenty-second year. It has been observed, principally in the sporadic cases, that the anterior fontanelle remains open till a late period.

There are no peculiar visceral lesions.

Pathology.—For our present knowledge of the pathology of cretinism as well as of myxoedema we are indebted to a number of investigators, but in particular to Gull, Ord, Sir V. Horsley, and Sir Felix Semon in this country, and to Kocher and Schiff abroad. Ord, in his original communications on the subject, specially noted the atrophy of the thyroid gland in myxoedema, the name applied by him to the cretinoid state described by Gull as developing in adults. Kocher independently described a peculiar condition, called by him *cachexia strumipriva*, which supervened after the operation of complete thyroidectomy. Sir F. Semon, struck by the resemblance of the condition described by Kocher to myxoedema, set on foot the investigation by the Clinical Society of London, which brought together a vast amount of evidence tending to prove the identity of this *cachexia* with myxoedema. Sir V. Horsley by numerous experiments shewed that a dyscrasia similar to *cachexia strumipriva* could be produced in some of the lower animals by thyroidectomy. Schiff shewed that the ill effects of thyroidectomy in animals could be diminished by transplanting a thyroid gland previous to the operation. The obvious resemblance of the mental and bodily changes in cretinism, first, to those observed in cases in which the whole thyroid gland has been surgically removed, and, second, to those in myxoedema which, like sporadic cretinism, was found to be nearly always associated with an atrophied thyroid gland, thus pointed to the conclusion that the essential cause of cretinism was the loss of function of the thyroid gland. The proof of this was completed when it was shewn that administration of thyroid substance was successful in removing the symptoms of the disease.

Symptoms.—At first it is probably thought that the child is simply backward, and it is not until the child is nine months or a year old that it is recognised that there is anything seriously amiss mentally and bodily. But in some cases the child has seemed normal for the first few years, and then has fallen into the cretinoid state. It ceases to grow, its features alter, and it becomes dull and stupid. To these latter cases the term *juvenile myxoedema* has been specially applied. In them the thyroid gland has probably at first been normal, and subsequently has undergone an atrophic change.

The following description applies to the cretinoid condition when fully developed. The child is always stunted in growth and dwarfed in stature, being usually between 3 and 4 feet in height when it has ceased to grow. Exceptionally the height may be as much as $4\frac{1}{2}$ feet,

and sometimes it is less than 3. Moreover, there is a want of proportion between the various parts of the body, so that there is a large plump head, a short deformed body, and thick podgy arms and legs, the latter being often crooked. The large head is flat at the top, spread out at the sides, narrow in front, and broad behind. The face is broad, stolid, and expressionless, and is often lined with wrinkles. The complexion is pale, sallow, waxy, or of a chalk-white colour. The forehead is low and broad. The eyes, which are small and dull but usually straight, appear half closed from the drooping of the swollen lids, and are wide apart, being set back at the ends of a furrow running across the root of the nose. The nose is broad, short, and stumpy, depressed at the root, and flattened and *retroussé* at the extremity, whilst the alae are thickened and the nostrils widely opened, as in the negro. The cheek-bones stand out, and the cheeks are loose and flabby, but do not shew the flush so commonly seen in myxoedema. The ears are large and thick, although usually normal in shape. Exceptionally, the lips are well formed, but are usually coarse, everted, protruding, thick, and blubber-like, and the angles of the mouth are rounded. The mouth is usually open, and the tongue, swollen and lolling, projects from the opening. There is usually dribbling of saliva or drooling. The lower jaw is thick and broad. The neck is short and thick, and in many cases large fatty masses may be felt and seen above the clavicles. The head often hangs forward on the chest, the erector muscles being too weak to support its weight; this produces a curvature of the cervical and upper dorsal spine. The breast is strikingly flat, and the chest is round and expanded at the base, whilst the costal angle is wide. There is usually bowing of the lower dorsal and lumbar spine, and the abdomen is characteristically large, protuberant, and pendulous. There is frequently an umbilical hernia. The hips are small and the limbs are short and thick. The hands are broad, short, and podgy, and their skin is thick, especially on the dorsum, and wrinkled. The legs are often bowed, the ankles are enlarged, and the feet are thick and square. The nails are short, thickened, cracked or chinky, and ill-shaped. The skin is yellowish-white, dry, branny, and rough to the touch. It feels doughy from the thickening of the subcutaneous tissues, and is loose and hangs in folds over the abdomen and at the flexures of the joints. Sweating is exceptional, but absence of perspiration is not so constant as in myxoedema. Moles or pigment spots or patches of a yellowish or brown colour or warts are not uncommon on various parts of the body. The hair is short and scanty, and is coarse, dry, straight, and sometimes bristly, more like horse-hair than that of a human being. In adult cretins it is usually absent on the body. The eyebrows are often scanty, but may be well formed: The scalp is dry and scurfy, and is sometimes covered with yellowish or brownish crusts. The teeth are late in appearing and soon become carious. In sporadic cases there is usually no evidence of the presence of the thyroid gland, but there may be enlargement of the gland or a goitre, and this is common in the endemic cases. The temperature is subnormal; the child is always cold,

likes to be near the fire, and is very sensitive to any fall in the thermometer. In cold weather the exposed parts of the body become blue. The bowels are frequently obstinately constipated, and the breath has a disagreeable odour. The urine is usually large in amount, but is otherwise normal. There is generally control over the sphincters, and when there is a sufficient degree of intelligence the patients are cleanly in their habits. The blood shews little change in corpuscular elements, but there is usually deficiency in the amount of haemoglobin, which may be no more than 50 or even 40 per cent of the normal. In some cases there has been a tendency to haemorrhages, especially from the nose. The intellectual condition of the cretin is always extremely low. The mental capacity varies from that of a low-grade idiot on the one hand to that of a child of four or five years old when the cretin is grown up, so to speak. The cretin does not learn to talk or to walk at the usual time, and does not attempt to move about like an ordinary healthy child. Sometimes, so far from learning to walk, it remains unable to stand or sit unless propped up and supported. In other cases it may only be able to move about by crawling on all fours. Eventually, however, the power of walking may be acquired, but the gait is waddling and clumsy. The power of speech sometimes remains altogether undeveloped. Sometimes the cretin cannot even cry or scream like an ordinary child, and expresses pleasure, anger, or fear by means of inarticulate grunts, howls or shrieks, barks or groans only. In course of time it may learn to say a few words, such as, "Yes," "No," "Mamma," or "Pussy," and it may learn to understand a little when spoken to. It may also learn the signification of gestures. A small number acquire a more extensive vocabulary, which is, however, very much restricted, and is composed almost entirely of monosyllables. Many of the consonants are very imperfectly pronounced. The voice is often harsh and hoarse. The cretin is usually dull of hearing; the degree of deafness is generally proportional to the stage of the disease. The deafness accounts for some of the mental dulness, and, to some extent, for the inaptitude for speech. Smell and taste are usually imperfect. Cretins often appear insensible to bad odours, and indifferent whether food is palatable or not. Sight is of all the senses the least affected. Usually it is normal, but the retina does not seem so sensitive to strong or dazzling light as in ordinary persons. The cretin has been observed to sit with the sun full in his eyes for a long time together.

In adultcretins the genital organs remain those of the child. There is absence of hair over the pubes, the axilla, and elsewhere on the body, and hair does not appear on the face in males. Males have a diminutive penis and small testicles, and females have the labia of little girls and an infantile uterus. The catamenia are absent or irregular, and sexual instinct is as a rule undeveloped. In high-gradecretins there may, however, be some evidence of development of sexual appetite and instinct.

Thecretins are usually good-natured and placid, and although stolid are easily amused. It is sometimes difficult to attract their attention by appealing either to the sense of hearing or sight, a somewhat cat-like

characteristic. They are apathetic and phlegmatic, and very slow and deliberate in all their movements. They are somnolent, and will sometimes sleep almost indefinitely if undisturbed. During sleep they breathe noisily. When awake they are lazy and inert. They will remain in the same position and play for hours without moving or taking any apparent interest in surroundings ; one cretin would take a full minute to raise her arm when asked to shake hands.

Duration.—The life of the untreated cretin is seldom, if ever, a long one. A number are carried off in the early years, and it is quite exceptional for an age of over thirty to be attained. Forty is probably the extreme limit. Death usually results from intercurrent disease, the specific fevers, pneumonia, bronchitis, erysipelas, heart or kidney disease, or convulsions.

Diagnosis.—In a characteristic case with the symptoms just described, diagnosis presents no difficulties and can usually be made almost as soon as the patient is seen and without asking any questions. The disease, however, is rare, so that many practitioners have never seen a case, and on that account sometimes fail to recognise the disease or suspect its existence when some other condition is present. One disease, *mongolian idiocy*, has some resemblance to cretinism, and several patients afflicted with it have been sent to me as they were thought to becretins. The mongolian idiot resembles the cretin in its stunted growth and undeveloped intellect ; the bridge of the nose is flattened, and the hands and feet are short and broad. The skin is rough and dry, and has given rise to the inappropriate designation of furfuraceous cretin. But there is no thickening of the subcutaneous tissues as in the cretin. The obliquely placed eyes, on account of which the name mongolian has been given, the finer features, and the greater alertness of mind and body are important points of distinction. The mongolian idiot is inclined to be restless, vivacious, mischievous, and destructive rather than stolid, slow, and inactive. *Achondroplasia* has sometimes been mistaken for cretinism, and Prof. Osler mentions that he was once asked to see two supposedcretins who proved to be suffering from this disease. The disproportion between the length of the limbs and the size of the head and body is its most striking feature. The long bones are very short, and their ends are much enlarged. The physiognomy is unaltered, the skin is natural, and there is usually an ordinary degree of intelligence (*vide Vol. III. p. 117*).

Infantilism is described in a separate article by Dr. John Thomson (*vide p. 486*). The ordinary forms of infantilism have little in common with cretinism. The features and the condition of the skin and of the intellect in ordinary infantilism serve to distinguish it sufficiently. The thyroid or myxoedematous form of infantilism is simply cretinism in a mild degree.

The slighter degrees of cretinism are those which are most difficult to diagnose, and when a child is not seen until after it has been treated by thyroid gland, it may be impossible to give a positive opinion. The

effect of giving and the effect of suspending treatment by thyroid gland will, however, establish the diagnosis.

Prognosis.—Under the thyroid treatment this is eminently favourable in early cases. Suitably conducted, it will certainly ensure rapid and complete bodily improvement, and though, as we shall see presently, mental improvement is not invariable, it is even more remarkable when it occurs. The earlier in life the treatment is begun the more complete and lasting appear to be the results. The treatment, however, in some form will have to be persisted in throughout the life of the patient.

Treatment.—"Not the magic wand of Prospero or the brave kiss of the daughter of Hippocrates ever effected such a change as that which we are now enabled to make in these unfortunate victims, doomed heretofore to live in hopeless imbecility, an unspeakable affliction to their parents and to their relatives." So wrote Prof. Osler in 1897 of the wonderful results of the then recently introduced thyroid treatment of cretinism, treatment which the further experience of later years has shewn to be as lasting in its results as it is successful. Textbooks published as late as even 1894 contain such statements as the following: "By far the greater number ofcretins arrive at their helpless condition by successive steps of degeneracy in their ancestors." "Treatment is very unsatisfactory." Unsatisfactory; it was worse than useless! Previous to the year 1891 there was neither help nor hope for the cretin. The remedy we now possess and know how to use was discovered in 1891, when Prof. George Murray announced his discovery, the effects of hypodermic injections of an extract of the thyroid gland of a sheep on cases of myxoedema, a discovery which was followed by that made in 1892 by myself and by Dr. E. L. Fox of Plymouth and by Howitz of Copenhagen independently that thyroid gland administered by the mouth was equally potent in dispelling the symptoms of myxoedema. The use of the remedy in cretinism quickly followed, and the results were found to be even more remarkable.

The preparation of thyroid gland which I have found most satisfactory in practice has been the tabloid prepared by Messrs. Burroughs Wellcome and Co., in this country. The dose which has to be given varies in different cases, and no definite hard-and-fast rule can be laid down as to its amount. In commencing treatment we must feel our way. If too large a dose be given great constitutional disturbance may be produced. Even a dose of 5 grains has made the patient very ill, causing fever, excitement, restlessness, headache, sleeplessness, vomiting, depression, and general pains in the body and limbs. A small dose, 1 grain of thyroid tabloid or 1 minim of liquor thyroidei, is sufficient to start with, and this should be cautiously repeated at short intervals, treatment being suspended when any undesirable symptoms are observed. In one case a dose of $1\frac{1}{2}$ grains given every third day has sufficed to effect a cure and afterwards to keep the patient well. In another, gradually increasing doses up to 3 grains a day were found necessary. Sometimes as much as 10 grains daily has been required, and a smaller dose has not sufficed.

In one of my patients a dose of 10 grains a day has now been taken for the last twelve years. Probably 5 grains a day may be considered as an average dose necessary to keep the patient well when the symptoms of the disease have all disappeared. As in the case of myxoedema, the remedy must be regularly taken during the whole of the patient's life. Should the remedy be suspended, myxoedematous symptoms gradually reappear. One of the most remarkable effects of the treatment is that the growth, which has been so completely arrested, almost immediately recommences. It is not unusual for a young cretin to grow several inches in six months. Growth has been observed to start again even incretins of twenty-five or thirty years of age. The rate of growth, however, is greatest in the early months of the treatment. As has been pointed out by Dr. John Thomson, growth is in inverse ratio to the stage of the treatment and the age of the patient. Children grow much more than adolescents, and adolescents than adults. A young cretin may grow 5 or 6 inches in the first year, 4 or 5 inches in the second, and then continue to increase in height at the normal rate. In the case of adolescentcretins it has been observed that the growth of the bones has not been accompanied by an increase in firmness, but, on the contrary, there has been softening, and the weight of the body has caused the legs to bend, and deformity closely resembling that of rickets has resulted. The bowing of the legs so produced has sometimes greatly interfered with the power of walking. It is only when the patient begins to use the legs that the bowing comes on. Accordingly cretins whose bones shew signs of bending should be kept lying down.

The results of treatment are of course most satisfactory in cases in which it is commenced early. When the disease has remained untreated for years, partial success only can be expected. It is impossible to give back the patient his lost years. The cretin of twenty can be considerably improved, but will remain deformed in body and dwarfed in intellect. It should, however, be impossible in the twentieth century that any cretin should be left long untreated.

When the discovery of the sovereign remedy was made cretins of all ages and in all stages were brought for treatment. For many of them the discovery had, unfortunately, come too late. Thus, such a case as that described by Dr. Coutts of a young man of twenty-four years "looking like a child of two, under 3 feet in height, entering the room with one hand clasped in his mother's and the other clutching a doll," was only too common. For such cases some degree of benefit would result from treatment, but that was all. Still, for some the remedy, although it came late, made all the difference between a useful existence and a living death. One of the most gratifying of my cases was a typical cretin who had reached the age of eleven when in 1893 the thyroid treatment was started. He grew very rapidly at first, and developed into a normal child except that his legs were disproportionately short. He has progressed satisfactorily in every way, and has gone on successfully from school to one of the universities. He always, however, remained about five years behind those of his own age.

He is now, at the age of twenty-five, in every respect a normal individual. The only evidence of his former condition is that he is of short stature, being only 5 feet 4 in height.

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MYXOEDEMA

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SYNONYMS.—*A Cretinoid State supervening in Adult Life in Women* (Gull); *Cachexie pachydermique* (Charcot); *Cachexia thyroidea*; *Cachexia strumipriva* or *thyropriva* (Kocher).

Description.—Myxoedema is the result of loss of function of the thyroid gland. It is characterised by marked changes in the general metabolism of the body as shewn by the functional alterations in the skin and its appendages, in the subcutaneous tissues, and the central nervous system. In the ordinary or primary form of the disease the loss of function is due to atrophy with fibrosis of the gland. In the secondary form the malady is induced by a total removal of the gland by operation for disease. Myxoedema in early life is known as cretinism or infantile myxoedema (*vide p. 334*).

History.—The history of myxoedema, though short, is full of interest. Attention was first drawn to the symptoms of the disease in 1873 by Gull, who called it "A Cretinoid State supervening in Adult Life in Women" allied to sporadic cretinism as previously described by Hilton Fagge. Four years later W. M. Ord recorded the symptoms observed by himself in five cases, with the post-mortem appearances, including an advanced stage of atrophy of the thyroid gland, found in one of them by Prof. W. S. Greenfield, and the result of the chemical examination of the skin by C. Charles. As Charles found an excess of mucin in the skin, Ord proposed the name myxoedema, by which the malady has since been known. In 1882 J. L. Reverdin described a peculiar chain of symptoms which he had observed to follow total extirpation of the thyroid gland for goitre. The following year Kocher of Berne also described this condition as *cachexia strumipriva*, although he attributed it to injuries to the structures in the neck and not to the loss of the thyroid gland. Shortly after this Sir Felix Semon, who noticed the remarkable similarity between the symptoms of myxoedema, as described in this country, and those of *cachexia strumipriva*, as recorded in Switzerland, suggested that they were really identical, and that both conditions, as well as endemic and sporadic cretinism, were due to the loss of function of the thyroid gland. In order to follow up this suggestion, the Clinical Society of London appointed a Committee to investigate the subject. The experimental work was carried out by Sir Victor Horsley, who by experiments on monkeys and other animals conclusively proved that *cachexia strumipriva* was caused by removal of the thyroid gland. The report of this Committee contains an exhaustive account of the subject of inquiry, and clearly shews that myxoedema and

cachexia strumipriva are identical, that cretinism is myxoedema occurring in early life, and that all these maladies are due to loss of function of the thyroid gland.

The symptoms of the disease having thus been traced to loss of the thyroid gland, the next advance was in the direction of supplying the deficiency. Schiff had already shewn that the usual fatal result of thyroideotomy in the dog could be averted by a preliminary transplantation of another thyroid gland into the abdomen of the animal, and von Eiselsberg proved that the same result could be obtained in the cat, provided the graft was successful. Quite independently, in 1890, thyroid grafting was suggested by Sir Victor Horsley as a method of arresting the disease in man. This suggestion was acted upon by several surgeons, especially by Bettencourt and Serrano, who noticed that in their case the operation was immediately followed by improvement, which they attributed to absorption of the juice of the transplanted thyroid gland. This observation appeared to me to be extremely important, as it indicated that the thyroid gland carried on its function by means of an internal secretion. I therefore concluded that if this was the case the regular use of the secretion, obtained in the form of an extract of the gland, would remove the symptoms of myxoedema, and suggested this line of treatment at a meeting of the Northumberland and Durham Medical Society in February 1891. In order to test this a glycerin extract of the sheep's thyroid gland was prepared, and injected at intervals beneath the skin so as to ensure its absorption by the lymphatics in the same manner as the normal secretion is conveyed into the circulation from the healthy gland. The symptoms of myxoedema in the first case I treated in this manner rapidly disappeared, thus proving that the thyroid gland is a true internal secretory gland, and that thyroid extract is a specific remedy for myxoedema. The following year it was shewn by Howitz, of Copenhagen, and by Dr. Hector Mackenzie and Dr. E. L. Fox, in England, that the same results could be obtained by the simple method of giving thyroid extract or the raw gland itself by the mouth.

Etiology.—The exciting cause of the fibrotic atrophy of the thyroid gland, the morbid change present in the great majority of cases, is unknown. In rare cases other diseases, such as syphilis and actinomycosis, have attacked the gland and led to an arrest of function and so to the appearance of myxoedema. There are, however, certain disposing causes, which may be considered under the following heads:—

Age.—Myxoedema may appear at any time of life from infancy to old age. Infantile myxoedema has, however, special features of its own, which are described elsewhere (art. "Cretinism," p. 334), so that here our attention will be confined to the malady as it appears in adolescents and adults. In order to ascertain the age at which myxoedema first appears, I tabulated 312 cases from various sources, 34 of these cases being males and the remaining 278 females. The age at which the disease first appeared varied from fifteen to seventy years. Taking the cases in women alone, it was found that an increasing number occurred in each succeeding

quinquennial period from fifteen up to forty-five, after which the numbers decreased. More than half (165) of the patients were between the ages of thirty and fifty, and more than one-third (98) between thirty-five and forty-five. Thus it is evident that between thirty and fifty, and especially between thirty-five and forty-five, is the period of life most favourable to the onset of the disease in women. Nearly two-thirds (21) of the male cases manifested symptoms first between thirty-five and fifty, which is therefore the usual period for the onset of the disease in the male.

Sex.—As in other forms of thyroidal disease, women are much more prone to suffer from myxoedema than men. Out of my series of 425 collected cases 370 were women and only 55 were men. Myxoedema, therefore, occurs nearly seven times as frequently in women as in men.

Locality.—Myxoedema is seen mainly in the white races inhabiting temperate climates. It occurs in all parts of Great Britain, but is rather more common in the north of England and south of Scotland than in other parts of the country. It is, on the whole, uncommon in France, Germany, and Norway. It is fairly well known in Australia and America, though less common than in this country. It is rare in the tropics, and very rare in the coloured races. Beyond these general data there are no known local conditions which favour the onset of the disease.

Heredity.—Heredity does not, as a rule, appear to have much influence on the incidence of myxoedema. In some families a certain degree of disposition to thyroidal disease undoubtedly exists, but this is usually in the direction of the various forms of goitre rather than of atrophy. Although the great majority of cases of myxoedema are sporadic, two or more have occasionally occurred in the same family; thus, in several instances, two and even three sisters, or a brother and sister, have suffered from the disease. It may appear in both a mother and daughter, or an aunt or a cousin of the patient may also be affected.

Personal Antecedents.—Neither social position nor domestic surroundings appear to have any influence on the incidence of myxoedema. It is rather remarkable that neither syphilis nor alcoholic excess, both of which commonly cause fibrosis of other organs, appears to play any part in the production of myxoedema. The only disease which is known occasionally to have a distinctly disposing effect is exophthalmic goitre, as in a certain number of cases recovery from this disease has been followed by the onset of myxoedema. This sequence of events occurs because one natural mode of recovery from exophthalmic goitre is, by a gradual involution of the hypertrophied thyroid gland, accompanied by fibrosis. In some of these cases this beneficent process proceeds too far, and results in an atrophic fibrosis of the gland with myxoedema. Excessive child-bearing has been regarded as a disposing cause of the disease, but the influence of this factor can only be slight.

Morbid Anatomy.—In almost all cases the *thyroid gland* is greatly reduced in size. One of my specimens weighed 3.5 grams (55 grains) and another only 4.5 grams (70 grs.) as compared with the average weight

in women, which is about 30 grams (1 oz.). The gland is pale in colour and tough in consistence, from the atrophy of the glandular cells and the formation of fibrous tissue. The microscopical appearance varies according to the stage of the disease; in the earlier stages the walls of the alveoli are infiltrated with small round cells, and the epithelial cells appear to be proliferating. In later stages the number of the alveoli is diminished, and there is a great increase in the amount of interstitial fibrous tissue. In very advanced cases hardly any alveoli can be found, the whole gland being converted into a mass of fat and fibrous tissue, which is obviously incapable of producing any secretion. The *parathyroid glands* have been found in one case examined by Dr. D. Forsyth to shew a marked tendency to form vesicles with a large amount of colloid secretion, associated with an increase in the amount of connective tissue in the stroma. These changes he regards as indicative of an attempt at an increased secretory activity to compensate for the thyroid insufficiency.

Skin.—The skin is thickened and somewhat translucent on section. There may be a partial atrophy of the epidermis. In the connective tissue of the corium bundles of nucleated fibrillae are seen to take the place of the normal trabeculae, and in some cases the spaces between the fibrillae are wide. The walls of the cutaneous vessels may be thickened by endarteritis. The sweat and sebaceous glands are partly atrophied. The hair follicles are surrounded by nucleated fibrous tissue, which in advanced stages of the disease contracts and so compresses the root sheath, which atrophies, and the hair is lost. In many cases there is an increase of fat in the subcutaneous tissue and in other parts of the body, such as the omentum.

In several cases the *hypophysis cerebri* has been found to be enlarged up to double its normal size, but in two of my cases it weighed 9½ grains, which comes within the normal limits of weight (5 to 10 grains).

Circulatory System.—In early cases no special changes are found in the heart or blood-vessels. In the advanced cases a condition of interstitial myocarditis may be found associated with fatty or fibroid change of the heart muscle. Atheroma is common in the aorta and larger arteries, and endarteritis in small vessels in various parts of the body.

No definite lesions have been found in the *nervous system*. The changes described in isolated cases are probably not directly related to myxoedema.

Genito-urinary System.—A moderate degree of fibrosis of the kidney is common, and may be accompanied by some hypertrophy of the left ventricle. Granular kidney may lead to death when all the symptoms of myxoedema have disappeared under treatment. No other definite changes have been found at all frequently in other organs.

General Pathology.—A clear understanding of the functions of the thyroid gland is the key to the pathology of myxoedema (*vide p. 326*). The thyroid is a secretory gland furnishing an internal secretion, which passes by way of the lymphatics into the general circulation. Myxoedema

is the result of atrophy or removal of the gland and the consequent loss of this secretion. As already pointed out, the thyroid gland in advanced cases of myxoedema shews pronounced fibrosis with atrophy of the glandular structure, so that in these cases the gland is evidently unable to furnish any secretion at all. In the earlier stages of the disease the atrophy is only partial, so that the remaining portions of the gland are still able to supply a limited amount of secretion. Thyroidal secretion plays a very important part in general metabolism in health, as is shewn by the dire results which follow its suppression by removal of the gland in animals and in man, or by its destruction by disease in man. A condition of myxoedema can be induced in many lower animals by thyroidectomy. In the rabbit I have found that this operation is followed after a long interval by loss of energy, swelling of the subcutaneous tissues, dryness of the skin, loss of hair, with subnormal temperature, all of which are symptoms of myxoedema in man. Gley has shewn that when the parathyroids are removed as well, acute nervous symptoms appear. It seems probable that in many experimental thyroidectomies the parathyroid glands were removed at the same time, and that some of the symptoms are really due to the loss of these structures. Important results have been obtained from experiments on monkeys by Munk, by Horsley, and by myself. In bonnet-monkeys, however, two parathyroid glands are enclosed in the thyroid, and are therefore removed along with it. In these animals a fine tremor usually appears about five days after the operation, and is shortly followed by progressive apathy. The animal sits huddled up with all four limbs in a position of flexion at all joints. Tonic spasms and occasional clonic contractions of the muscles are common. Epileptic fits may also occur. The temperature gradually becomes subnormal. During the second and third weeks the myxoedematous swelling appears, and is most distinct in the face, the eyelids and lips becoming swollen. The skin becomes dry and rough, and the whole condition is remarkably like the myxoedema which develops acutely after total thyroidectomy in man. Since myxoedema can be produced experimentally in this manner, and since all the symptoms of the disease in man can be removed by the internal administration of thyroid extract, there can be no doubt that the disease is due to the gradual diminution and ultimate cessation of the normal supply of thyroid secretion.

Symptoms.—*The onset* of the first symptoms of myxoedema is usually so insidious that it is often difficult to ascertain their real duration. This is because the morbid changes in the thyroid gland develop extremely slowly, and the supply of the secretion fails very gradually. In secondary myxoedema, the symptoms may appear rapidly or slowly according as the removal of the thyroid gland has been complete or partial. In the former case, the symptoms may develop acutely within a period of a few days; in the latter case the acuteness of the onset will be proportional to the amount of secreting thyroidal tissue left. At the commencement of the disease the patient complains of gradually

increasing sense of languor, associated with disinclination for exertion. Thus, ordinary daily duties, which previously were performed without conscious effort, become extremely irksome. The more energetic struggle against this tendency but are conscious of the effort it entails, whilst others tend to limit their sphere of action more and more. There is also about this time undue sensitiveness to cold, which in cold weather especially is apt to induce the adoption of an indoor life of very limited activity. At this stage slight alterations take place in the facial appearance, due to the gradual development of the characteristic subcutaneous swelling. The face becomes somewhat rounded, the eyelids and lips slightly swollen, and there may be a slight flush in the centres of the cheeks. These changes take place gradually, and in the earlier stages do not cause the striking alteration in the aspect of the patient which we are accustomed to see in fully developed examples of the malady. At this time there may be some increase in weight, so that the change in appearance may be attributed to obesity. The skin becomes rather dry, though it may still be moist at times, and the hair may begin to come out to a slight extent. The temperature is usually normal or only slightly subnormal. On inquiry, it is not unusual to find that at quite an early stage of the disease the patient is subject to slight auditory and visual hallucinations. These subjective sensations are not so clearly defined as in the later stages. The progress of the disease may be arrested at this early stage, and no further advance take place for a long period. In the great majority of cases, however, the symptoms gradually become more distinct until the disease is fully developed and assumes the form which we shall now consider in detail.

Solid Oedema.—The most characteristic symptom of myxoedema, and that to which the malady owes its name, is the swelling of the subcutaneous tissues. This swelling is most abundant where the subcutaneous tissues are lax, and so imparts a peculiar appearance to the face and hands of the patient. On palpation the swelling feels somewhat more elastic in consistence than ordinary adipose tissue, and does not pit on pressure. In the early stages of the disease it is only slight and causes no very striking alteration in appearance, but in advanced cases it may be sufficient in amount to add several stones to the weight of the body. The face as a whole becomes full and rounded, and the skin of the eyelids and infra-orbital regions looks translucent and distended as if with watery oedema, as is well shewn in Fig. 5, which was taken from a man at the age of 48, fifteen years after the first onset of the disease, who, however, did not come under my observation until ten years later. The cheeks are thick and rounded, and the centre of each is reddened owing to dilatation of the minute venules in this region. The subcutaneous tissues beneath the chin are often considerably thickened. The lips are thick and everted, and the nose and ears are also swollen. The tongue is often considerably enlarged, and causes in part the peculiar alteration in the speech which is often quite characteristic. As a result of the swelling the upper eyelids tend to droop, and to compensate for

this there is an instinctive contraction of the occipito-frontalis muscles, with well-marked transverse wrinkling of the forehead. The normal mobility of the face is lost, and so advanced cases of myxoedema have a fixed mask-like expression, which varies but little with passing emotions.

The swelling is often present to a notable degree in the supra-clavicular fossae. Over the trunk and limbs it is uniformly distributed, and its full extent is not always realised until after it has been removed by treatment. The backs of the hands are usually much swollen and



FIG. 5.—Characteristic case of myxoedema in a man 48 years old, fifteen years after the onset. Before treatment.

form a contrast to the palms, where the swelling is scanty. The hands appear to be broad and relatively short. The range of movement of many joints is limited by the solid oedema. This is noticed chiefly by the patient in such movements as fastening a collar at the back of the neck or stooping to lace up the boots, whilst some of the finer movements of the fingers, such as are required in doing needlework, can no longer be executed.

Cutaneous System.—In the early stages of the disease the skin gradually becomes dry and the superficial layers of the epidermis are shed more readily than in health. In consequence of this the insides of the

stockings, when removed at night, look as if they had been sprinkled with some fine white powder like flour, owing to the presence of numerous fine dry scales of epidermis. In more advanced stages the skin becomes very dry as sensible perspiration gradually ceases, and even insensible perspiration is so much diminished that only half the normal amount of water may be lost as aqueous vapour. The skin of the face and neck in some cases is yellowish in colour, which, combined with the red flush on the cheeks, helps to make up the characteristic facial appearance in myxoedema. The skin covering the palms of the hands, the soles of the feet, and the extensor surfaces of the elbows and knees is especially thick, rough, and dry. Warts and pigmented moles are present on the skin in some cases.

Some loss of hair may occur in quite the early stages of myxoedema. In advanced cases almost all the hair may be absent, the head being quite bald, as in Fig. 5, and the eyebrows and eyelashes quite scanty. When bald the skin of the scalp is often dry and scaly. If the hair is not lost it becomes finer in texture. The nails also give evidence of malnutrition, and are often cracked, grooved, and discoloured.

The *mucous membranes* are paler and less translucent than in health. The lips are usually swollen and dry, and the mucosa of the mouth, nose, and throat is also often dry.

The *thyroid gland* in the great majority of cases of myxoedema is diminished in size, and the longer the duration of the disease the smaller the gland. In cases of some duration in which the subcutaneous swelling has been removed by treatment little or no isthmus can be felt in front of the trachea, and the lateral lobes cannot be made out. In a few cases the gland has been found to be larger than normal; it is, however, but rarely that the diminution in functional activity is accompanied by an increase in size.

In the early stages of myxoedema the *temperature* may be quite normal, or only slightly subnormal. In later stages patients are very sensitive to cold, and in winter complain that they are unable to keep warm. The hands and feet feel cold to the touch. Such patients are much more comfortable in summer or in a warm climate. In fully developed cases the temperature is nearly always one or two degrees below normal, and in some it may be as low as 95° F., or even 93°. In fatal cases it has fallen as low as 77°, or 66° shortly before the end.

Mental Symptoms.—All sufferers from this malady shew more or less mental hebetude. They are slow in fully comprehending a new subject, or in carrying out any new line of thought or action. About one-fourth of the cases shew a tendency to spend an undue amount of time at the same employment, and so may dawdle away an hour in dressing in the morning or in eating a meal. The memory is deficient for recent events, but is not apparently affected in regard to those which occurred before the onset of the disease. The temper is usually good, though there may be irritability at times. Many patients are acutely sensitive in regard to the alteration in their appearance, and in consequence become shy and

retiring. This tendency, added to the general hebetude, leads in advanced cases to a secluded and indoor life. Sleep is generally sound at night, though it may sometimes be disturbed by dreams, and there is often drowsiness during the day. Visual and auditory hallucinations are often very vivid in advanced cases, and even in quite early cases they occur in a less realistic form. In slight cases, ill-defined objects, which are compared to a mouse running across the floor of the room, are seen, or noises are heard. In advanced cases well-defined figures are seen, which sometimes can hardly be distinguished from those of real persons. They may take the form of near relations or of entire strangers. Voices are heard to speak distinctly, or familiar sounds, such as that caused by the opening of a door, may be heard, either separately or in association with the visual phenomena.

Insanity.—A few advanced cases of myxoedema, when they were untreated, became insane. When treatment is commenced in the early stages of the disease this rarely occurs. The peculiar mental symptoms just described may gradually become intensified until the patient becomes insane. Acute or chronic mania, melancholia, or dementia have developed in such cases. The special tendency to avoid observation may pass into a condition of suspicion. The mental weakness is apt to increase until finally dementia combined with general weakness is established. In other cases irritability, doubt, or exalted ideas may be present, and there may be terminal convulsions and coma immediately before death.

Special Senses.—In about one-half of the cases the sight is found to be defective ; in many of them, however, this is due to causes unconnected with myxoedema. In a small number of cases watering of the eyes and a general diminution in acuity of vision may be attributed to the malady itself. Hearing is found to be diminished in about 50 per cent of the cases. One or both ears may be affected. Occasionally the deafness is nearly complete, but disappears as the result of treatment by thyroid extract. The senses of smell and taste are diminished in about one-third of the cases. Sexual feeling is usually diminished or in abeyance, though certainly one case has been recorded in which a man with myxoedema married and became the father of two children.

Sensory Symptoms.—In addition to sensations of cold due to the depressed temperature, frontal and occipital headaches, neuralgic pains and prickling sensations are felt in various regions of the body. Attacks of aural vertigo and tinnitus occur in some cases. Tactile sensation may be diminished, whilst appreciation of heat and cold is unaffected.

Reflexes.—The superficial reflexes are diminished but are rarely absent. The tendon reflexes are usually normal ; they are only exaggerated in the presence of some complication, such as lateral sclerosis, as in two cases which I have seen.

Circulatory System.—In slight cases of myxoedema there are usually no symptoms of cardiovascular disease. In advanced cases the symptoms of cardiac disease may be very severe. The chief symptoms in these

cases are dyspnoea on exertion, with palpitation, and in some cases severe attacks of syncope, one of which may prove to be fatal. The cardiac impulse is feeble and ill-defined, and the heart-sounds are distant, but no murmur is audible unless some valvular lesion is present as a complication. These cardiac symptoms in cases of myxoedema which have gone for long periods without treatment are due to fatty and fibroid change in the heart muscle. The recognition of this condition is of great practical importance, as when it is present treatment with thyroid extract must be carried out with great care. Even slight additional exertion undertaken by such patients during the early stages of the treatment has caused fatal attacks of syncope. Before I had realised this danger, one of my cases died in this way while walking up a hill, and another after stooping down to lace her shoes. The pulse is usually less frequent than in health, slow, and regular. When renal disease or arteriosclerosis is present the tension will be high.

Blood.—There is generally a moderate degree of anaemia, the red corpuscles being diminished in number and deficient in haemoglobin. As a rule the number of red corpuscles is reduced to between 3,000,000 and 4,000,000 per c.mm., and the haemoglobin to 60 or 70 per cent and occasionally to 40 or 50 per cent of the normal amount. Except for an occasional leucocytosis the white corpuscles are normal in number and appearance.

It is generally stated that *haemorrhages* from the uterus and mucous membranes are common in myxoedema. In the cases which have come under my own observation, however, I have not found any special haemorrhagic tendency.

Alimentary System.—Loss of appetite and constipation are common. The lips, gums, and tongue are more or less swollen, according to the severity of the case. The tongue is sometimes so large that when it is protruded it fills the space from one angle of the mouth to the other. The teeth are generally carious and the gums may be soft, spongy, or ulcerated. Many patients complain of a thick mucous discharge which runs from the mouth during sleep. (*Vide Vol. IV. Part II. p. 208.*)

Genito-urinary System.—In the early stages of the disease the urine is generally quite normal. In advanced cases, however, it may be pale in colour, have a lowered specific gravity varying from 1008 to 1018, and contain a diminished amount of urea. In about one-fifth of the cases there is albuminuria, which in many of these is due to the myxoedema, as it entirely disappears under treatment by thyroid extract. In others it persists and is due to fibrosis of the kidney. Albumosuria has been observed by Fitz. In some cases menorrhagia occurs during the early stages of the disease, though more commonly amenorrhoea is present. In some this is of course simply due to the age of the patient, in others, however, it is a result of the myxoedema, as menstruation has been re-established after treatment. Pregnancy seldom occurs after the onset of myxoedema in a woman, but it must be remembered that the disease very frequently first appears at or about

the time of the menopause. In a man sterility is not a necessary result. In both sexes the external organs of generation may be somewhat swollen, and the skin covering them is dry as in other parts of the body. The pubic hair is usually scanty, and may be lost in advanced cases.

Natural Course and Prognosis.—The course of the disease and the duration of life have been so entirely changed by the present method of treatment that it is necessary to describe shortly the natural course of myxoedema when palliative treatment only was available. The natural course of the disease was very slow, so that a patient might be incapacitated by the disease and yet survive for years. Thus, in a series of 320 cases, which I collected from various sources, the disease lasted for less than five years in 147, for five to nine years in 90, for ten to fourteen years in 50, for fourteen to nineteen years in 20, whilst 13 cases lived more than twenty years. As many of these cases were alive at the time they were recorded, the duration given here does not represent the full duration of the disease in all cases. The general tendency of the disease was to get progressively worse, though the condition sometimes remained stationary for several years, and temporary improvement, especially during warm weather, was not uncommon. Death not infrequently occurred from some acute disease, such as influenza, pneumonia, or bronchitis, which the patient was unable to resist. Cardiac failure from chronic degeneration of the myocardium, granular kidney with arteriosclerosis, cerebral haemorrhage, and insanity were the immediate cause of death in some cases, and in others death was apparently due to the progressive degeneration entailed by the disease itself. The prognosis was, therefore, gloomy, as no prospect of recovery could be held out. A certain amount of relief could be afforded by palliative treatment, and the course of the disease might be slow, but sooner or later it was certain to progress to a state of chronic invalidism with a fatal termination.

Since the introduction of the treatment of the disease by thyroid extract, its course has been profoundly modified. All the symptoms of the malady can be removed by the administration of sufficient doses of the extract, and they do not return if the supply is adequately maintained. Provided the treatment is started early and maintained throughout, a patient with myxoedema may now live as long as any one else. Thus, my first case is still alive and well though it is more than seventeen years since she first began the treatment, simply because she continues to take the extract without intermission. In the case of educated people this good result may naturally be expected, but hospital patients are apt to be intermittent in their attendance, and relapses will occur from time to time from interruption of the treatment. As soon as treatment is resumed, however, the symptoms again disappear. The prognosis now is therefore very good, as with continuous and adequate treatment good health may be enjoyed for many years. If the case be one of long standing, in which either chronic degeneration

of the myocardium or renal disease was present before the commencement of treatment, the prognosis must be framed according to the degree of these complications.

Diagnosis.—In cases of fully developed myxoedema the appearance of the patient is so striking that the diagnosis can usually be made immediately on inspection (*vide* Fig. 5). Such cases are now rarely seen, and the diagnosis, which has now to be made in the early stages of the malady, may sometimes be rather difficult. Careful attention to the presence of the symptoms already described as occurring in the early stages of the disease will aid the formation of a correct opinion. The colour of the complexion, the shape and expression of the face, the dryness of the skin, associated with loss of hair and the presence of hallucinations, are all valuable indications of the development of the malady. From ordinary obesity, with which of course it may be combined, the translucency of the swelling of the eyelids, the state of the skin and hair will usually distinguish it. *Adiposis dolorosa* is sometimes mistaken for myxoedema, but in this disease the swelling does not affect either face, hands, or feet, and is due to the formation of irregular masses of fat in various parts of the body, which are painful and tender on pressure. In acromegaly the face is long and oval instead of being rounded as in myxoedema, and the enlargement of the face, hands, and feet is due to a definite increase in size of the bony and other structures, and not merely to the thickening of the subcutaneous tissues by the solid oedema. In early cases in which the presence of myxoedema or of benign hypothyroidism is suspected, but the diagnosis is not certain, recourse may be had to the therapeutic test. If the patient be given full doses of thyroid extract for three or four weeks the symptoms will greatly diminish or disappear if they are due to myxoedema; if no improvement takes place it may be safely concluded that they are due to some other cause.

Treatment.—In the treatment of myxoedema the deficiency of thyroid secretion must be made good by the internal administration of some suitable preparation of the thyroid gland containing the secretion in an active form. This treatment is conveniently divided into two stages, the object of the first being to remove entirely all the symptoms of the malady, and of the second to maintain the patient in health, for it must always be remembered that abandonment of the treatment at any time will sooner or later be followed by a return of the symptoms of the disease. The two official preparations of the thyroid gland may be most conveniently employed. These are the original thyroid extract, liquor thyroidei, and dry thyroid, thyroideum siccum, 1 grain of the latter being equivalent to 6 minims of the former. In most cases the liquor gives the best results, but it should be freshly prepared once a fortnight. It should be prescribed undiluted, and the patient be instructed to measure out the required dose in a minim-glass and add a dessertspoonful of water. The dry thyroid may be given as a powder or tablet, and should be employed in relatively larger doses than the extract. It is

advisable to begin the treatment of a case with a dose of 5 minims of the extract or 2 grains of the powder each night at bedtime. This dose may be gradually increased up to 10 or 15 minims unless the pulse is unduly accelerated. The full dose should be maintained until the first stage of the treatment is accomplished and the symptoms have disappeared. During the second stage, which lasts during the rest of the patient's life, a daily dose should be given which is just sufficient to maintain good health without any recurrence of the symptoms. This permanent dose varies in different cases, according to the amount of thyroidal atrophy present, from 5 to 15 minims. As a rule a daily



FIG. 6.—The same patient as in Fig. 5, after three months' treatment with thyroid extract.

dose of 10 minims of the extract or from 3 to 5 grains of the powder will be found to be fully adequate. If the disease has reached an advanced stage, and especially if any symptoms of cardiovascular degeneration are present, rest in bed should be enjoined during the first stage of the treatment, as there is a risk of cardiac failure if any increased effort be made at too early a period of convalescence. Fortunately, at the present time the disease is usually recognised at an early stage, so that this precaution is now rarely necessary.

Under the influence of this treatment the symptoms of myxoedema all gradually disappear, and the change in the appearance of the patient is striking. This is well illustrated by Figs. 5 and 6. In this case the disease had probably been developing for some fifteen years before

treatment was commenced at the age of 48. The gradual diminution of the myxoedematous swelling is accompanied by loss of weight, which may amount to as much as two or even four stones. The skin becomes moist and soft, and hair begins to grow afresh. The temperature rises to the normal level, both mental and physical activity are restored, and mental symptoms may entirely disappear. In women who have not reached the menopause menstruation is re-established. In short, the symptoms entirely disappear and the patient recovers, remaining free from all symptoms of myxoedema as long as the treatment is continued.

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EXOPHTHALMIC GOITRE

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SYNOMYMS.—*Graves' Disease, Basedow's Disease, Basedow'sche Krankheit, Glotzauge-Kachexie, Cachexie exophthalmique, Goitre exophthalmique, Morbo di Flajani, Gozzo esofthalmico, Bronchocele exophthalmica.*

Definition.—A disease characterised by enlargement of the thyroid gland, protrusion of the eyeballs, rapid action of the heart and palpitation, and tremors of the extremities. With these may be associated an irritable and excitable condition of the nervous system, loss of flesh, increased action of the skin, flushing, anaemia, derangement of the catamenial function, and other troubles.

Etiology.—*Sex.*—Graves' disease affects females much more frequently than males. This is the case in childhood as well as in later life, a contrast to cretinism, which affects nearly as many males as females. Although the disease is certainly comparatively uncommon in the male sex, somewhat varying estimates of its relative incidence have been given by different authorities. It is possible, although not probable, that the proportion in the two sexes may vary considerably in different countries. According to Charcot the disease is only a little less frequent in men than in women, and according to Eulenburg the proportion of female to male cases is two to one. In this country the proportion is certainly very different, and probably the opinions of these authorities were founded on insufficient data. Among 212 cases under my observation there have been eighteen males, and among Prof. George Murray's 180 cases there were ten males. This gives a proportion of thirteen females to one male. Relatively rather more male cases are seen in private than in the hospital practice, and of recent years the proportion of male cases I have seen has been somewhat higher than formerly. Buschan, among 980 cases collected from various sources, found 805 females and 175 males, a proportion of nine to two. A possible explanation of this is that on account of their comparative rarity male cases are more frequently reported than female.

Whilst the disease may arise at any age, it is chiefly between puberty and the menopause that it occurs. Children are comparatively seldom attacked, and I have not observed a case in a patient under twelve years of age. But the disease has been recorded in children as young as two and a half years more than once. Out of 495 patients whose ages have been recorded by Buschan, 15 only were under ten years of age and 31 only were over fifty years of age. The age distribution of the remaining patients was as follows:—38 were between ten and sixteen years of age, 352 were between sixteen and forty years of age, of whom 163 were

between twenty and thirty years of age, and 69 were between forty and fifty years of age.

The disease sometimes affects several members of the same family, or it may occur in successive generations. I have met with many instances of this as well as of the association of ordinary goitre in one member of a family with the exophthalmic form in another member. Some striking examples have been recorded, such as Rosenberg's series, in which grandmother, father, two aunts, and two sisters were all affected, and Oesterreicher's, in which eight children out of a family of ten and three grandchildren were all the subjects of Graves' disease.

The malady is often consequent upon acute disease, and a number of cases appear to have followed an attack of influenza. Quinsy, rheumatism, and a tendency to bleeding, especially in the form of epistaxis, have been observed as preceding events in the history of a significant number of cases. Severe fright, intense grief, great anxiety or worry, and other causes of mental strain or profound emotional disturbance have long been recognised as antecedents of the disease. It is interesting to note the close connexion between some of the chief symptoms of exophthalmic goitre and the more immediate effects of terror. The descriptions given by Darwin and Sir Charles Bell of the condition presented by persons under the influence of intense fear at once suggest the symptoms of exophthalmic goitre. The heart beats quickly and violently, so that it palpitates or knocks against the ribs. There is trembling of all the muscles of the body. The eyes start forward and the uncovered and protruding eyeballs are fixed on the object of terror; the skin breaks out into a cold and clammy sweat, and the face and neck are flushed or pallid. The intestines are affected.

Whether or not any swelling of the thyroid gland ordinarily accompanies these symptoms arising from terror I do not know. But I may observe that, as was known to the ancients, in the adult female the thyroid gland may temporarily become swollen under the influence of great excitement. That, occasionally, Graves' disease, in a well-marked form, rapidly follows a severe and sudden shock to the nervous system, suggests that the starting-point of the disease may be a derangement of the emotional nervous system, and that with this there is sooner or later associated an altered or perverted condition of the thyroid gland, which serves to keep up many of the characteristic symptoms.

The association of the disease with other nervous disorders, either in the patient or in other members of the same family, has often been pointed out. Chorea, hysteria, epilepsy, diabetes, acromegaly, and insanity are some of the diseases with which it thus has relations. The disease has sometimes occurred simultaneously with tabes dorsalis, paralysis agitans, disseminated sclerosis, or idiopathic muscular atrophy, but I have never met with an example of these.

Whether the malady has any close connexion with chlorosis is uncertain, but undoubtedly the latter frequently accompanies it in young women. Occasionally the disorder shews itself for the first time during

pregnancy or after parturition. On the other hand, as I have observed in several instances, great improvement or even recovery has resulted from pregnancy. Disorders of menstruation sometimes precede the disease, and possibly have some causal relation with it. Osteomalacia has been seen in association with Graves' disease.

Some have looked on Graves' disease as an auto-intoxication ; others regard it as reflexly excited by some local morbid condition in the nose or elsewhere. Tuberculosis and Graves' disease have been considered by some to be antagonistic. I can only recall one case in which Graves' disease occurred in a tuberculous subject, and that was only in a mild form. On the other hand, L. Levy found 13 cases of Graves' disease among 170 tuberculous patients ; such an experience must be quite exceptional.

Graves' disease affects persons of all classes of society. In the case of women occupation has not appeared a factor of much importance, but among men I think it has influenced the production of the disease to some extent. It is significant that several of my male patients have been engine-drivers or station-masters placed in situations involving mental strain. It appears to be on the whole as prevalent in one country as another ; but some localities furnish more cases than others. Thus, certain parts of Kent, Surrey, Wiltshire, and the Thames valley have produced a relatively large proportion of the cases under my observation. In districts where ordinary goitre prevails, the exophthalmic form is also more common than in other parts.

Morbid Anatomy.—On post-mortem examination, general emaciation is usually first to be noted. The prominence of the eyes is seldom so evident as during life. It has been observed in some cases that the fat deposited in the orbits is greater in amount than normal. An increased amount of connective tissue in the neck, enlarged cervical and bronchial glands, and swelling of the lymphatic structures of the intestines, have sometimes been present. According to Kocher, swelling of the lymphatic glands in the neighbourhood of the thyroid is a constant feature of severe Graves' disease. The swelling is merely hyperplastic. The spleen is occasionally enlarged.

The heart may be normal, dilated, or hypertrophied, or it may be the seat of valvular disease, the result of old endocarditis which has arisen independently of the disease. The lungs are free from disease unless there be accidental complications, of which pneumonia is the most common. There are usually no naked-eye changes in the nervous system.

The *thyroid* usually shews uniform enlargement. It has been alleged that the thyroid gland in this disease is very vascular. The vascularity is, however, principally superficial. The veins over the capsule are numerous and dilated. The nutrient arteries are also large, tortuous, and dilated. Professor Greenfield observes that in cases examined by him there has been no increase in the vascularity of the gland itself, but rather a diminution. Mr. Edmunds, however, states that a remarkable hypertrophy of the blood-vessels is sometimes found, and Mr. F. T. Paul

is of opinion that the vascularity of the gland is decidedly greater than in other forms of goitre. The vascularity of the gland seems to be simply the result and the concomitant of increased activity, and will vary according to the stage of the disease. For this reason it is more likely to be observed in the specimens removed by the surgeon than in those which are obtained in the post-mortem room. The enlargement of the gland is general. On section the tissue is firm but elastic, and the surface is coarsely granular and has a brownish colour; its consistence at an early period is less, at a later is greater, than that of the ordinary gland. Sometimes there are irregular swellings due to encapsulated masses of tissue in which are numerous islands of colloid material. As a rule the follicles are found empty of colloid material. The iodine content of the gland has been investigated by Oswald and Albert Kocher. In cases in which the follicles are empty the iodine content is much below that of the normal gland. Sometimes hardly a trace of iodine is to be found, but in cases in which colloid material is present in the follicles an extraordinary quantity of iodine has been found, as much as 40 to 50 milligrams in one lobe (*vide p. 326*).

On microscopic examination the main feature is the increase of secreting structure. The vesicles, instead of being, as they are normally, round or square, are branched or stellate, and their lining membrane is involuted, so that there are papillary projections into the spaces. The secreting structure, moreover, is not merely increased, but is much altered. The epithelium lining the vesicles is changed in form from cubical to columnar. The colloid matter which normally fills the interior of the vesicles has partly or entirely disappeared, its place being taken by a mucoid substance which stains badly. Desquamation of the epithelium is not uncommon, so that the vesicles contain detached columnar cells. In addition to the changes in the vesicles there may be seen a number of newly formed tubular spaces lined by a single layer of cubical epithelium, like the tubules of a secretory gland, and Professor Greenfield has pointed out the resemblance in appearance of the goitre to a salivary gland. The goitre, according to him, bears the same relation to normal thyroid that the mammary gland during lactation does to the resting gland. Mr. W. Edmunds has shewn the striking similarity between the microscopical appearances of gland-tissue in exophthalmic goitre, and in the case of an animal which has had a large portion of the thyroid removed by operation. After the operation the small portion left behind undergoes changes of the nature of compensatory hypertrophy. A section of this altered gland is practically indistinguishable from one from the thyroid of a case of Graves' disease. From this it seems probable that in Graves' disease the thyroid, for some reason at present obscure, takes on increased functional activity.

At a later period when the gland has become firmer from the growth of fibrous tissue, the proliferative changes mentioned may be obscured or absent.

The persistence and enlargement of the *thymus* gland is certainly a

very frequent if not a constant feature of the disease. Isolated cases were recorded by Markham and Goodhart many years ago. In all the cases in which I have had the opportunity of seeing or making an autopsy, the thymus gland has been persistent, and many pathologists have noticed persistence of the thymus in fatal cases of Graves' disease. The thymus gland in these cases consists of two flat triangular fleshy bodies lying behind the manubrium sterni, and reaching down to the pericardium, over the upper part of which they are sometimes spread out like an apron. The microscopical appearances of the thymus in Graves' disease differ in no way from those of the ordinary gland, and there is the usual structure, including the corpuscles of Hassall. The persistence of the thymus in these cases is difficult to explain. Possibly every case in which there is a thymus persisting into adult life is one of potential or latent Graves' disease.

Alterations in the sympathetic have been described by some pathologists, but it has not been shewn that the changes found are in any way peculiar to exophthalmic goitre. Prof. Greenfield describes swelling of the ganglia with marked hyperaemia in the more superficial parts, active invasion of the tissue by leucocytes, and degenerative changes in the ganglion cells.

As regards the central nervous system, minute haemorrhages in the neighbourhood of the medulla have been observed (Greenfield, and Hale White); but beyond these, which are in all probability secondary changes, the result and not the cause of the disease, there is nothing of importance. A most careful and thorough examination of the pons, medulla, and other parts was made at St. Thomas's Hospital in a case in which there had been ophthalmoplegia externa and hemiplegia, but no microscopical changes were found.

Pathology.—Many hypotheses have been propounded to explain the peculiar symptoms of this disease. It has been ascribed to an altered condition of the blood, to an affection of the sympathetic, to a derangement of the emotional nervous system, to a disorder of the nuclei about the fourth ventricle, and finally to the diseased condition of the thyroid gland itself. No characteristic changes in the blood have been found to be constantly present, and it cannot be shewn that anaemia stands in any causal relation to the disease. Whilst the sympathetic ganglia, in some cases, have been found diseased, this is not a constant feature. Only some of the symptoms of exophthalmic goitre could be produced by an affection of the sympathetic, and it is impossible to formulate a satisfactory hypothesis of the malady on this basis. The assumption that there is a derangement of the emotional nervous system would account for most of the symptoms, but not for the enlargement and over-activity of the thyroid, nor for the persistence and hypertrophy of the thymus.

The same may be said as regards a disorder of the nuclei in the neighbourhood of the fourth ventricle. Too much importance has been attached to a few, still unconfirmed, experiments on animals by Filehne, who stated that in one case he produced exophthalmos, enlargement of

the thyroid, and increased cardiac action, by dividing the anterior fourths of the restiform bodies. Minute haemorrhages in the medulla are found in a number of affections besides exophthalmic goitre—in myxoedema, for example—and as above suggested are the result, not the cause of the disease. No mere limited lesion of the bulbar nuclei could explain the widely spread character of the symptoms.

Since a knowledge has been gained of the great functional importance of the thyroid gland, the hypothesis that exophthalmic goitre is due to disease of this organ has had many adherents. Möbius was one of the earliest to put forward and support this opinion.

As has been stated above, the gland has an increased blood-supply, and it is evident from the microscopical appearances that there is increased secretory activity with hyperplasia of the epithelium. It may with reason be inferred from this that an amount of thyroid secretion greater than usual will be discharged into the circulation. If the change in the thyroid be the cause of all the symptoms of the disease we should expect to find in it the reverse of the picture in myxoedema. The contrast which the two diseases present has been dwelt on by many writers, and especially by Möbius. Comparing the myxoedema patient on the one side with the subject of exophthalmic goitre on the other, we see many points of contrast. One patient, the myxoedematous, gets more and more bulky, the other, while the disease is active, steadily loses flesh. The one is intolerant of cold, the other of heat. The skin of the one is dry and swollen, of the other moist and shrunken. The temperature of the one rarely rises above the normal; that of the other rarely if ever falls below it. The one is slow, placid, and deliberate; the other quick, irritable, and impulsive. The heart's action in the one is quiet, in the other rapid. We know that the secretion of the thyroid gland when administered to a patient in large doses, either by subcutaneous injection or by the mouth, has the power of increasing the rate of the heart's action, of causing loss of body-weight, and of stimulating the action of the skin. It raises the subnormal temperature of the myxoedematous patient to the normal or above it, and in over-doses produces vomiting, headache, and violent pains in the limbs. Although no instances of the production of exophthalmos in human subjects by the administration of the thyroid gland have been observed, Mr. W. Edmunds has succeeded in causing exophthalmos in dogs and monkeys in this way. If dogs or monkeys are fed with large doses of thyroid glands, there results acceleration of the heart's action, increased metabolism, loss of weight, sweating, and exophthalmos.

It would seem, then, that the hypertrophy and over-activity of the thyroid is the cause of the symptoms of the disease and of most of the changes in the organs of the body, just as the atrophy and loss of activity of the gland is the cause of myxoedema or its non-development is the cause of cretinism. What it is that starts the hypertrophy of the thyroid and what part the persistent thymus plays we do not know. In some cases the disease seems to be set up by shock or by emotion which

we know may be followed very shortly by swelling of the thyroid gland. It is possible that the disease may sometimes be due to microbic infection. Kocher has suggested that an increased metabolism in the nervous system, such as might be produced by sudden or prolonged nervous exhaustion, brings toxic substances through the circulation to the thyroid gland, and so gives rise to irritation and reaction causing increased activity of the parenchyma.

Some have supposed that the primary disease may be in the para-



FIG. 7.—A case of Graves' disease in an active stage. Patient, a man of forty, who had been ill six months. Five years later he was in good health and leading an active life. He had gained two stone in weight, the goitre had nearly disappeared, and the eyes were much less prominent.

thyroids. The resemblance of many of the symptoms of exophthalmic goitre to those of athyroidea, which has been attributed by some to removal of the parathyroids, has been pointed out by Mr. W. Edmunds and others. Exophthalmos, however, has not been observed to follow removal of the parathyroids during the short time which the animals survive this operation. More recent investigations have not lent support to the belief that the parathyroids are of great functional importance. Moreover, no characteristic changes in the parathyroids have been observed in cases of Graves' disease.

Symptoms.—The symptoms mentioned in the definition as character-

istic of the disease may come on simultaneously or may gradually appear one after the other. The thyroid enlargement, combined with the protrusion of the eyes, renders the disorder easy to recognise. Sometimes the first sign of anything amiss is an alteration in temper, the patient being easily worried or unduly irritable. With this is soon associated functional disturbance of the heart. Thyroid enlargement, although probably present from the first, may not be observed till a later period. As time goes on the symptoms increase in severity; palpitation is more constant and more distressing, the eyes are more obviously prominent, the swelling of the thyroid gland is greater, the patient becomes more excitable and irritable and has attacks of trembling, the body wastes, and flushing, sweating, and other symptoms are added to those previously present.

We shall proceed to consider the various symptoms in detail, and then discuss the varieties of the disease, its course, and its duration.

When the patient is first seen the *goitre* is, as a rule, of moderate size, but it may be very large or so small as hardly to be discernible. The swelling usually comes on very gradually, but sometimes it attains a considerable size within a short space of time. The enlargement of the gland is usually more apparent on the right side than on the left, just as the right lobe of the normal thyroid is larger than the left. Very rarely the left lobe is the larger, and still more rarely the enlargement is entirely one-sided. The swelling is generally soft and uniform, but it may be irregular and firm and hard, with round or nodular masses embedded in it. The latter condition is likely to be met with where a goitre has existed previous to the onset of the other symptoms of the disease. The enlarged gland may be seen or felt to pulsate simultaneously with the vessels in the neck, and on palpation a systolic thrill is often perceptible. On listening with the stethoscope a long whiffing systolic or continuous murmur may be audible over the gland, like the venous hum in the neck in anaemia. Often the goitre has not been noticed by the patient until the doctor has looked for it and pointed it out, but it will probably have been observed that the collar or the dress was too tight round the neck. The goitre itself seldom causes serious inconvenience and very rarely produces pressure symptoms. During the course of the disease the goitre varies in size. The swelling of the gland may temporarily increase after excitement or over-exertion or at the catamenial period. It may also slowly and steadily increase for a time, and then gradually diminish, or it may repeatedly increase and diminish. With a diminution in size of the thyroid there may be general improvement in the patient's condition, but this is not always the case. There is no necessary relation between the intensity of the symptoms and the size of the gland, and in some of the most severe forms of the disease thyroid enlargement is inconspicuous.

The Eyes.—The exophthalmos, like the thyroid enlargement, varies in amount in different cases. In well-marked cases the eyeballs appear as if starting out of the head. Occasionally the protrusion is so great that

the eyelids cannot voluntarily be closed, nor do they meet in sleep. On the other hand, it may be so slight as to be hardly perceptible, even to the trained observer nothing more than a slightly staring look being noticeable, or it may be absent altogether. The exophthalmos is often unequal on the two sides, and it may be quite unilateral. Like the thyroid enlargement the prominence of the eyes may vary from time to time during the course of the disease, and may be affected by the same causes. Moreover, it may come on very gradually, or appear so quickly that within a short time the eyes appear to be bolting out of the head.

Two important signs have been described in connexion with exophthalmos; these are known as von Gräfe's sign and Stellwag's sign. Von Gräfe's sign consists in the lagging of the upper eyelid in downward movement of the eyes. To obtain it the finger or a pencil should be held horizontally in front of the eyes of the patient, who should be directed to follow it while it is gradually lowered. If the sign be present the upper eyelids lag, not closely following the movements of the eyeballs, so that the sclerotics may become visible between the lids and the corneae. Von Gräfe's sign, although generally present, may be absent. It is not peculiar to the subjects of Graves' disease, but may be observed in other individuals, and it is possible to produce the sign voluntarily.

Stellwag's sign consists in an increase of the width of the palpebral fissure due to the retraction of the upper lid, and with this is associated diminished frequency and incompleteness of winking under reflex stimulation. In consequence of the retraction of the lids, the sclerotic may shew all round the iris. The widening of the palpebral fissure is not a mechanical result of the exophthalmos, and is not directly in proportion to it. The diminished reflex excitability of the eyelids contributes to give the eyes their staring look. Stellwag's sign is one of the earliest as well as one of the most constant symptoms of the disease.

Möbius pointed out another eye symptom, namely, insufficient power of convergence for near objects. On convergence the patients experience a sense of strain, but have no double vision. This, however, is by no means a constant feature of the malady. A glistening, slightly oedematous condition of the conjunctivæ may frequently be noticed.

Occasionally some weakness of the external ocular muscles exists, so that there is slight drooping of both upper eyelids, or some paresis of the external recti, producing double vision on looking to the extreme right or left. Paralysis of the 3rd nerve and multiple paralyses of the eye muscles have been observed. In rare instances complete ophthalmoplegia externa has been recorded.

On ophthalmoscopic examination pulsation of the retinal vessels may be seen. This is sometimes limited to the vessels of the disc, but usually it is also visible in its neighbourhood. The retinal vessels are sometimes dilated and tortuous.

No defect of vision, as a rule, accompanies the exophthalmos, but besides the sense of straining which sometimes accompanies efforts at convergence, patients often complain of various subjective symptoms,

such as flashes of light before the eyes, and feelings as if the eyes were being pushed forwards.

On voluntary movements of the eyelids the latter may be affected with a fine tremor. Trembling of the eyeballs is also sometimes to be noted. Sometimes there is painful spasm of the orbicularis palpebrarum. When the spasm has been very severe dislocation of the eyeball has occurred; but this is very rare. Watering of the eyes is often a source of annoyance, and in some cases epiphora has been an initial symptom, but, on the other hand, there may be an abnormal dryness. Slight degrees of conjunctivitis are not uncommon.

Ulceration of the cornea occasionally, though rarely, occurs, and this may go on to sloughing of the cornea, perforation, panophthalmitis, and destruction of the eye. In a case under my observation, the perforation occurred quite painlessly, and the eye was lost before the patient made any complaint about it.

Accompanying the protrusion of the eyeballs and the afflictions of the lids already mentioned, in some cases there is swelling of the upper and sometimes also of the lower eyelids. Sometimes the swelling is not a true oedema, as it can be dissipated by causing contraction of the orbiculares by electric stimulation. Sometimes there is a kind of solid oedema which remains for a long period, even after many of the other symptoms of the disease have disappeared.

Elevation and arching of the eyebrows is generally to be observed when there is a high degree of exophthalmos. Pigmentation is often specially noticeable in the neighbourhood of the eyelids.

The disturbances of the circulation form characteristic and constant features of the disease. The heart's action is rapid. The rate varies in the slighter cases between 90 and 110 beats in the minute, and in cases of ordinary severity between 110 and 130. In severe cases the heart may persistently beat at the rate of 130 to 160 pulsations or even more in the minute. I have never met with an undoubted example of the disease in which the rate of the heart was not above the normal, but cases in which bradycardia supervened have been reported. The rapidity of the heart's action, moreover, is apt to be increased on slight exciting causes. The patients, as a rule, are painfully conscious of palpitation, and it is the chief trouble of which they complain. In some cases they have a feeling as if the heart were beating all over the body. Occasionally, however, there is a rapid cardiac action without the patient being uncomfortably conscious of it. The pulsation of the carotids in the neck is generally a conspicuous feature of the disease. On inspection, they can be seen beating forcibly and rapidly. Synchronous with the throbbing of the carotids there may be corresponding nodding movements of the head, as in aortic incompetence (Musset's symptom). As a rule the action of the heart is regular; but it may become irregular, and this is most likely to be the case when the disease is progressing unfavourably.

Often the increased cardiac action is accompanied by cardiac hyper-

trophy or dilatation. On inspection diffuse pulsation may be observed over the area of the praecordium, and on palpation a diffuse impulse may be felt. Both sounds of the heart are abnormally distinct, and the first sound is sometimes much accentuated. Systolic murmurs at the base of the heart and in the course of the great vessels are not uncommon. These are of functional origin, but sometimes there is evidence of organic valvular disease. As regards the radial pulse there is nothing constant in its character except its frequency. In different cases it may be hard or soft, strong or weak. The arterial blood-pressure has been found normal, or raised, or below normal, and its significance is doubtful.

Tremor is one of the cardinal signs of the disease. It varies, however, in degree. It may be the chief trouble of which the patient complains, or its presence may be recognised by the physician only on careful examination. If a patient, the subject of this disease, be asked to stretch out the extended hands, a characteristic tremor will be observed, consisting of vibratory movements of small amplitude, with a period of about one-eighth or one-ninth of a second. The tremor is of the same nature as that which may be observed in over-fatigued muscles in healthy persons. The tremor is a communicated one, and affects the whole extremity, not the fingers only. It may be observed in the leg as well as in the arm, and is usually equal on the two sides of the body, but in some cases it is limited to, or is more intense in, one limb. The tremor is generally more obvious when the patient is flurried, and sometimes may only be noticeable in such circumstances. It is more conspicuous when the patients are standing up than when they are lying down.

Besides this, finer tremor attacks of trembling may affect the whole of the body, such attacks bearing the same relation to the tremor that palpitation does to the rapid cardiac action. It is, as a rule, only when the tremor is aggravated that it interferes with the movements of the hands, and then the more delicate actions only are affected, such as writing, sewing, or buttoning a glove or dress. The patient will probably use the spoon or fork or carry a cup to the lips with perfect steadiness.

We shall now describe the symptoms which are usually associated with those of more special diagnostic importance already described.

Emaciation is a characteristic feature of acute cases, or of those in which the disease is active, and a loss of two or three stones is not uncommon. Sometimes the degree of emaciation is extreme, and the prognosis is then very unfavourable. The wasting of the body tissues which takes place in Graves' disease is not the result of diminished intake of food, as it may be observed in patients who throughout have taken their food well. It is related to the increased total as well as minimal metabolism of the body and to the remarkable increase of the consumption of oxygen and of the output of carbon dioxide mentioned on p. 331; as there stated in severe cases the increase of oxygen consumption amounts to as much as 50 to 70 per cent, an increase which, according to Magnus-Levy, "occurs nowhere else in the whole range of pathology." Only

part of the increase can be accounted for by the tremors, for the gaseous exchanges are increased during rest as well as at other times. As the disease subsides the patient regains flesh. Mild cases are sometimes met with in which the patients remain well nourished throughout.

Loss of strength is in proportion to the severity of the disease. Usually the patients are easily tired, but sometimes excitement will carry them through a great deal of exertion.

The temperature of the body, as a rule, is normal, but occasional slight degrees of pyrexia are not uncommon, the elevation generally not exceeding 1° or 1·5° F. I have had observations made with great care in a large number of cases, and find that a temperature above 100° F. is quite exceptional. Some observers, however, have recorded febrile cases. It is probable that pyrexia when present is due to some complication. Although the temperature may not be raised, a *subjective feeling of heat* is the rule. It is most troublesome at night when the patient is in bed, and even when the weather is cold she will feel warm with an amount of covering which a healthy person would consider quite insufficient. She likes cold weather and is very intolerant of heat.

Affections of the skin are of considerable interest and to some extent are always present. In the first place the patients often suffer from flushing of the head and neck, especially on excitement or when conscious of being under observation, but sometimes without any apparent cause. They have the feeling as if the blood were rushing to the head, and their face and neck become uncomfortably hot. A bright blush sometimes appears on the body as well as on the face. The sweat-glands are over-active, the skin is supple and moist, and free sweating may be excited by slight exertion. Sweating of the hands and feet may be a source of great annoyance to the patient. The increased moisture on the skin is no doubt the cause of the diminution of the electrical resistance of the body first pointed out by Vigouroux and Charcot.

Pigmentary changes in the skin are not uncommon. The complexion often suffers, and the skin of the face becomes sallow and sometimes muddy-looking. Sometimes there is a general bronzing of the skin, as in Addison's disease, or irregular patches of pigmentation appear on various parts of the body. The parts generally affected are the face, neck, the sides of the chest, the nipples, the abdomen, the lumbar region, the axillae, and the flexures of the arms and thighs. The colour of these parts is a more or less dark brown, a contrast to the normal colour of the skin to be seen on the front of the chest. Sometimes the pigmentation is limited to the eyelids.

Patches of leucoderma, vitiligo, or multiple telangiectases may sometimes be observed. The association of sclerodermia with Graves' disease has been recorded by several observers. There may be a fleeting oedema which appears and disappears quickly in various parts of the body.

Itching may be very troublesome and annoying, like that which occurs in jaundice or results from the administration of opium. That it is a toxic

symptom, due to the thyroid secretion, is shewn by the fact that similar itching of the skin is sometimes experienced by patients who are being treated medicinally with thyroid gland. The itching is sometimes accompanied by an urticarial eruption, which may become chronic. Factitious urticaria and erythema have also been observed.

The nutrition of the hair also generally suffers, and too much thyroid seems nearly as bad for the hair as too little. Many patients complain of the thinness, dryness, and falling out of the hair of the head. The hair of the eyebrows and eyelids and of the axillary and pubic regions may be similarly affected. I have seen total alopecia, and other cases have been recorded, but it has seemed to be doubtful whether this was not an associated condition rather than a consequence of the disease. The teeth frequently become carious during the course of the disease.

Anaemia is often present to a certain degree among the younger patients, but is not constant. That it may be a prominent feature of the disease is shewn by Begbie's belief that it was the primary factor in the malady, whilst Sir S. Wilks has cautioned the inexperienced to beware of mistaking cases of Graves' disease for ordinary anaemia. No important changes have been observed in the erythrocytes as the result of the disease, except diminished haemoglobin. Kocher states that in many cases a differential count of the white corpuscles shews an increase in the lymphocytes up to 60 per cent (in one case the proportion was as high as 74 per cent), but usually the proportion was from 30 to 40 per cent. Among the lymphocytes are many atypical forms, such as large mononuclears. Two to three per cent of myelocytes have been present.

Epistaxis sometimes occurs in the course of the disease as well as before it; of this I have seen a number of examples. Troussseau recorded pulmonary, intestinal, meningeal, and cerebral haemorrhages, but of these I have met with no instance.

Dreschfeld called attention to the occurrence of acetonaemia in connexion with attacks of persistent vomiting, to which reference will be made farther on.

In the *respiratory system* the chief troubles are nervous cough and attacks of dyspnoea. The cough is generally dry, like that observed in cases of ordinary goitre, and may be due to the pressure of the enlarged thyroid on the trachea and nerves adjoining. As the result of cardiac weakness the patient is apt to suffer from shortness of breath on exertion. Rarely there occur attacks of dyspnoea which are attended with aggravation of all the symptoms, swelling of the vessels of the neck, blueness of the face, and impending asphyxia. Such attacks have at times proved fatal, and recently I have had a case which terminated in this way after repeated attacks. It has been supposed that they arise from a sudden increase of direct pressure of the goitre on the trachea; and this is supported by the resemblance they bear to the similar attacks which arise in cases of aneurysms pressing on the trachea or main bronchi, and by the evidence that the trachea bears of having been compressed

laterally. Attacks of dyspnoea of a similar kind are, however, observed in the condition known as athyroidea, and it is therefore improbable that they depend merely on mechanical causes. A symptom referred to by American authors as Bryson's symptom is by no means characteristic, and is only exceptionally met with. This consists of greatly diminished expansion of the chest in inspiration.

Oedema of the lower extremities is not infrequent as a result of cardiac weakness. General oedema may occasionally be one of the main features of the disease at an early stage, and there may be effusions into the serous cavities as well as anasarca. Sometimes local oedema has been observed, such as that already referred to as affecting the eyelids. Oedema sometimes affects one side more than the other: this is independent of position, and is associated with vasomotor disturbances. In some cases as the disease is subsiding the lower extremities become much thickened from solid oedema infiltrating the subcutaneous tissues. Such non-pitting swelling was first described by Basedow, and is probably of the same nature as the swelling which is observed in myxoedema. It occurs in patients who, instead of getting thinner, appear, as the result of the disease, to gain in bulk. In these cases the circumferences of the thighs and calves are much increased, and some of the patients have told me that they find it difficult to get stockings large enough to fit them.

The *digestive functions* are nearly always altered in some way or other. The appetite is often capricious, and the patient, like a pregnant woman, has longings for unusual kinds of food. Sometimes the appetite is ravenous, and the patient can hardly wait for the conveyance of the food to the mouth. On the other hand, especially when the disease is progressing unfavourably, there may be more or less complete anorexia. There is often excessive thirst. The increased metabolism accounts to some extent for the abnormal appetite and the excessive sweating for the thirst. Vomiting, apparently unrelated to the ingestion of food, is not uncommon, and sometimes becomes a grave symptom. In the latter event the patient complains of epigastric pain, and can retain nothing on the stomach. In 7 cases in which such attacks have occurred. Dreschfeld observed that the breath had a peculiar sweet odour, and that the urine not only smelt of acetone, but gave the characteristic reaction for diacetic acid. With the vomiting there is intense prostration, restlessness, and the dyspnoea or air hunger observed in diabetic coma. Fortunately these symptoms not infrequently pass off, but they occasionally end in death. Looseness of the bowels is frequent. It is apt to come on without apparent cause, and as a rule is unattended with griping. The patient may have four or five loose motions in the course of the day, and this may continue for a week or a fortnight at a time. Sometimes acute attacks of diarrhoea may supervene, which completely prostrate the patient and occasionally prove fatal. Sometimes vomiting and diarrhoea occur together.

Intermittent albuminuria, generally considerable and sometimes ex-

cessive, has been recorded by Warburton Begbie and others, but cannot be considered as a common feature of the disease. Sometimes polyuria and sometimes glycosuria have been observed. Alimentary glycosuria can be more readily produced in patients with Graves' disease than in normal persons. In most cases, however, the urine is normal in amount, and free from albumin and sugar.

The catamenial function is not infrequently deranged during the course of the malady. Irregularity of menstruation, amenorrhoea, and menorrhagia are common, but in some cases the function is normal. Female patients frequently suffer from leucorrhoea.

The existence of the disease does not appear to offer any obstacle to the occurrence of pregnancy. As has been pointed out, patients frequently improve during pregnancy, and generally go to full time. In some of the cases under my care severe flooding occurred after delivery. As a rule in them also the influence of pregnancy was favourable; although I have observed cases in which the symptoms of the disease have appeared for the first time during gestation.

Nervous System.—A change in the mental condition is often one of the earliest symptoms, although one meets with cases now and then in which the patient remains placid, good-tempered, and generally amiable. The intellectual powers may remain unimpaired. It is characteristic of the disease that the patient in many cases becomes abnormally irritable, excitable, emotional, fidgety, and restless. She longs for continual change, and feels she must constantly be seeing or doing something new. She may be uncomfortably conscious of this alteration, and will tell the physician all about it, or, what is perhaps more common, he only hears of it through the patient's friends. At one time she is low-spirited and lacrymose, at another she is buoyant and smiling. She is inclined to be wayward and wilful, and to resent being thwarted or contradicted. She is readily upset by any unusual occurrence. A sudden loud knock at the door, or the arrival of a telegram, may throw her into a state of great agitation, perhaps lasting for hours. She is profoundly affected by the receipt of good or bad news. Sometimes there is insomnia, or the sleep is disturbed and unrefreshing; the restless patient tosses about in bed, is troubled with disagreeable dreams, and is apt to wake up in a fright. Sometimes she walks in her sleep, or jumps out of bed and wakes to find herself on the floor. The moral nature is sometimes perverted, so that the patient becomes spiteful, untruthful, suspicious, and generally discontented.

In some cases more serious mental changes supervene, the patient has delusions or hallucinations, or gets ideas of persecution, or becomes quite insane. Melancholia and mania are the usual forms which the insanity assumes. Such cases are usually fatal, but they are not common, for I can recollect one case only which required removal to an asylum.

Headache is frequently complained of, but presents no peculiar features. Those affected with the disease are also liable to neuralgias of

various kinds. I have seen several cases in which facial neuralgia has been a troublesome and obstinate symptom.

The tremor or trembling, already mentioned as one of the cardinal symptoms, belongs, of course, to disorders of the nervous system. Among the less common nervous symptoms are painful cramps. These occur in the extremities, especially in the hands and feet; they commonly come on in the feet and legs at night-time. As a rule, these cramps do not last long; but occasionally I have observed more persistent spasm in which the hands assume the characteristic form seen in tetany.

The tendon reflexes are present and are generally brisk. Patients sometimes experience a giving way of the legs when walking or standing. They feel their knees suddenly giving way, and they either fall or with difficulty just avoid doing so. It is interesting to notice that the same symptom is common in myxoedema. A decided feebleness in the lower extremities, almost amounting to paraplegia, has been observed in some aggravated cases of the disease. Hemiplegia, monoplegia, and multiple neuritis have also been observed, but these are decidedly rare.

Varieties of the Disease ; Course and Duration.—A well-marked case of Graves' disease is readily recognised at first sight. The malady is typical when all the four cardinal symptoms—goitre, exophthalmos, rapid cardiac action, and trembling—are present. When the chief symptoms are present, many of the minor symptoms will also be found present. Of the chief signs, exophthalmos is that by means of which the nature of the case is usually recognised.

It must be borne in mind, however, that the disease is often incomplete, and in its slighter forms may easily be overlooked. The most important and most essential symptom is the rapid cardiac action. The goitre and the exophthalmos may be present in very varying degree. The enlargement of the thyroid may be so slight that the patient may never have been conscious of it, and at the time she comes under the observation of the physician both it and the exophthalmos may escape notice.

Trousseau expressed an extreme view when he said : "I believe that the disease may be foreseen, and does really exist in a great number of instances without there being exophthalmos, bronchocele, or extreme frequency of the pulse." Without at least one of these features with some of the associated symptoms, I do not consider the diagnosis of the disease can be made. There is no doubt, however, that incomplete forms of the disease (*formes frustes*), to which Charcot and Marie first drew special attention, are not uncommon. Two varieties of the disease may thus be described—the *complete* and the *incomplete*. The mode in which the symptoms of the complete form of the disease make their appearance throws light on the incomplete form. In some cases all the four main symptoms appear more or less simultaneously. More commonly, however, one or two symptoms shew themselves first. Thus, rapid cardiac action with tremor and palpitation and some of the secondary symptoms may first appear, and exophthalmos or goitre, or both, follow later. Indeed,

the malady may subside without the appearance of the latter, and the case is then an incomplete one. Sometimes exophthalmos is the first symptom to appear, sometimes it is the last. Most commonly the goitre is the first sign of the disease. The incomplete form is characterised by rapid action of the heart, tremor, and nervous irritability, with which are probably associated some swelling of the thyroid and slight ocular symptoms.

Again, the disease may be divided into *the acute* and *the chronic* forms ; the latter of common occurrence, the former more rare. In the acute cases the symptoms may disappear within a few days. A number of the reported cases have been in quite young children. In a case recorded by Moore, the symptoms, which appeared in a young girl on reading a letter telling of her brother's death, lasted only two days. Solbrig has reported a case of a boy aged eight, who, after suffering from palpitation, enlargement of the thyroid, and prominence of the eyes, entirely recovered after twelve days. In a girl of ten years the duration was six weeks (Müller) ; the symptoms were awkwardness in the movements of the hands, frequent vomiting, lassitude, and pains all over the body followed by exophthalmos and swelling of the thyroid. Numerous cases have been related in which the duration has been no more than three or four months. Besides these cases of short duration followed by recovery, there are others in which the illness has ended fatally within six weeks of the onset. The acute cases are, on the whole, rare ; and fortunately recovery is more common than death.

A considerable number of the chronic cases begin more or less acutely ; and in the course of a chronic case acute symptoms may appear, so that no hard-and-fast distinction can be drawn between the two forms.

An important clinical division is into the lean type and the fat type, or as we may call it, the *forme maigre* and the *forme grasse*. The patients who are well nourished and remain so do well ; the thin patients nearly always cause us anxiety.

Another division may be made into *primary* and *secondary* cases. The secondary cases are those in which the disease occurs in a patient who has previously suffered from ordinary goitre ; these cases are not uncommon.

Marie proposed the barbarous title goître Basedowifié and Kocher the name Struma Basedowiana or Gravesiana colloides for these secondary cases. These cases, as pointed out by Kocher, are generally comparatively mild ; exophthalmos may be wanting, but tachycardia is constant.

Whilst the duration of the acute cases varies from a few days to a few months, that of the chronic cases is, as a rule, to be measured by years. I have had cases under my care in which the duration of the disease has been over twenty years.

Relapses are not uncommon. Sir W. Gowers speaks of a patient who had three attacks at intervals of several years. Troussseau relates the case of a lady who, for the sixth time during six years, presented all the symptoms of the disease, and each time was much benefited by

hydropathic treatment. Dr. Huggard of Davos Platz has shewn me a lady who relapsed repeatedly on leaving the high altitudes, and finally presented some of the symptoms of myxoedema. Relapses may come on after years of apparent recovery. In the cases of relapse observed by myself it has seemed to me that the disease has really never subsided; and that the relapses were rather exacerbations or recrudescences than recurrences of the malady. The possibility of relapse must be taken into consideration in making a prognosis.

A *sequel* to exophthalmic goitre which has now been observed in a significant number of cases is myxoedema. Occasionally the two conditions seem to be combined: the symptoms of myxoedema supervening while those of exophthalmic goitre are still present. Sometimes myxoedema follows closely on exophthalmic goitre, but there may be a long interval between the times of onset of the two diseases.

Death may terminate the malady either as its direct result or from intercurrent disease. The end may be sudden and due to syncope, even in the case of patients who are apparently going on well. Thus, Dr. Hale White mentions the case of a young woman, an in-patient in the hospital but not ill enough to be confined to bed, who, seeing the electric current applied to another patient, asked that it might be tried on herself. On the application of the current she fell back dead, having been laughing and talking only an instant before she died. It is, however, more usual to have some previous evidence that the case is not progressing satisfactorily. A form of marasmus occasionally ensues and the patient becomes greatly emaciated and prostrated. In this condition death may result from cardiac failure or from exhaustion following on persistent vomiting, diarrhoea, dyspnoea, or acute mania.

In about half of the fatal cases the end comes from intercurrent diseases, such as pneumonia, bronchitis, and cardiac disease. The disease may prove fatal at any stage. Death may occur within a few weeks of the onset or not until the disease has lasted many years.

Diagnosis.—There is no difficulty about the diagnosis when the symptoms of the disease are well marked. Characteristic cases can only be overlooked as the result of too cursory an examination. The combination of symptoms which have been described, goitre, exophthalmos, tachycardia, and tremor, ought not, however, to be mistaken for any other disease. It is very different when the case belongs to the incomplete or fruste form. Neither goitre nor exophthalmos is an essential symptom, but the presence of one or other in some degree is necessary for a positive diagnosis of Graves' disease. Cases of tachycardia should be carefully examined for thyroid enlargement and for ocular symptoms, and if these be entirely absent a diagnosis of Graves' disease cannot be made with certainty; but if one be present the case is almost certainly one of incomplete Graves' disease. I have not yet seen a case which I should admit to be one of Graves' disease in which tachycardia was entirely absent.

Prognosis.—It will be gathered from what has been said as to the

course of the disease that a guarded prognosis must necessarily be given. The duration, the course, and the end of the disease in any individual case are uncertain. Relapse may occur even after the apparent subsidence of the disease. The more severe the symptoms the greater will be the anxiety as to the issue. Progressive emaciation, much prostration, great rapidity of the heart's action, anorexia, continued vomiting, severe diarrhoea, dyspnoea, excessive muscular tremor, must all be looked on as symptoms of grave omen; on the other hand, many cases present a mild course throughout, and in these a hopeful prognosis may be given with some confidence.

The disease is, as a rule, so long drawn out that many cases are lost sight of, especially in hospital practice; and a good deal of uncertainty thus prevails as to the issue of them. I have tabulated the result in thirty-three patients under my own care in whom the disease either lasted over five years or ended fatally, and Dr. R. T. Williamson has done the same in 24 cases observed at the Manchester Infirmary.

Result in Fifty-seven Cases.

	My own Series.	Dr. Williamson's Series.	Total.
Fatal termination	.	8	6
Recovery complete	.	5	5
Recovery almost complete	.	9	2
Improvement considerable	.	9	4
Improvement slight	.	1	3
In statu quo	.	1	3
Alive, but exact condition not known	0	1	1

Out of 900 cases collected by Buschan, a fatal result was recorded in 105. In about 25 per cent of the cases death results from the disease. In about 50 per cent, more or less complete recovery will eventually take place. In the remainder the disease continues in a chronic form during life. There does not seem to be any rule as to the duration of the malady, the symptoms of which may last from a few months to many years.

Even when recovery takes place, the disease as a rule does not leave the patient as she was before the attack. Rousseau remarked that swelling and induration of the thyroid with prominence of the eyeballs always remained behind. For most cases, no doubt, this is true; but sometimes the exophthalmos quite disappears as well as the goitre, and this is more likely to happen if the exophthalmos has been moderate and the goitre small. The longer exophthalmos lasts, and the more pronounced it is, the more probable is it that it will be permanent.

The prognosis of exophthalmic goitre in children is more favourable than in adults. Some of the little patients recover completely; whilst in others, as in adults, a little enlargement of the thyroid and slight exophthalmos remain without other troubles. In those cases which have ended fatally, death has resulted from intercurrent affections, and not from the disease itself.

Treatment.—The natural course of the disease is so variable that there is great difficulty in correctly interpreting the effects of treatment. Under similar conditions as to treatment some cases improve rapidly, some remain stationary for a long time ; others fluctuate, or steadily lose ground, and end fatally. It is not surprising that a great many remedies have been employed for such a disease, and that there should be much difference of opinion as to their value. Hygienic measures are of great importance. The first essential when there are signs of serious illness is to give the patient rest of mind as well as of body. As long as the patient is losing flesh the rest should be absolute, for the strength has to be husbanded as much as possible. Remembering how impressionable the patients are, we should endeavour to keep away from them all disquieting influences. The physician can help them with encouragement and cheer them with the hope of recovery by and by, but it is his duty to let the friends clearly understand that the duration of the illness may be long, and that time is an all-important element in battling with the disease.

Of hardly less importance are an abundant supply of fresh air and good and judicious feeding. Open-air treatment is perhaps more easily carried out in the case of Graves' disease than in almost any other disease, since the patient is particularly tolerant of cold, disliking hot and stuffy rooms and thoroughly enjoying being out in the fresh air. At St. Thomas's Hospital it has been my custom to keep the patients out of doors on the balconies all day long, and I have found that this has proved highly beneficial to them. The diet should be carefully regulated. It will be found that the patient has sometimes a craving for most unsuitable articles of food, such as nuts, pickles, shell-fish, pastry, and ices. Such things should be strictly prohibited when they take the place of wholesome and nutritious articles of diet. Meals should be taken at regular intervals, and the food should be plain, wholesome, and well-cooked. Treatment by means of milk obtained from goats deprived of their thyroid glands, which is considered on p. 382, has a bearing on the dietary of patients suffering from Graves' disease. As this milk appears to contain something possessed of therapeutic value, it is, in my opinion, not judicious to give patients large quantities of milk and meat from animals with the thyroid gland in full functional activity. Accordingly, I have of late restricted the amount of ordinary milk to small quantities only, and have almost entirely excluded meat from their dietary. I allow all kinds of fish, fat bacon, chicken, eggs, vegetables, salads, fruit, cream, sugar, butter, bread, and carbohydrates generally. Under this diet the patients seem to do well, and, as far as I can see, the diet is good and suitable both in practice and from a priori considerations. Tea and coffee should be allowed with discretion, and in small quantity. The patient, as a rule, is better without alcohol. The disease being so rare in men, it is almost superfluous to say that tobacco should be forbidden in all its forms.

In the less severe forms of the disease a moderate amount of exercise in the open air is beneficial. Dancing, sight-seeing, visiting theatres

and picture-galleries, and shopping should be prohibited. If the patient be sent away to some health resort, special injunctions in regard to this matter should be laid down; as the benefits of the change of air and scene may be altogether counterbalanced by the excitement of social entertainments.

When a patient is able to be up and about, change of climate, air, scene, and surroundings may prove beneficial. The change should be as thorough and as restful as possible, but no absolute rule can be laid down as to the place to which a patient with Graves' disease should be sent. One case will do well at the seaside, another inland, one at a high elevation, another at a low, and it is impossible to predict what will suit a given case. The patient's own experience on this point is a help in arriving at a decision. I think I have seen more cases benefit by residence at the seaside than elsewhere. Sometimes, however, the seaside is too exciting and too stimulating. In summer the glare of the sun may be very trying, and shelter from the sun and wind and protection from dust should, if possible, be obtained. It is obvious that where the disease has arisen at the sea-coast a change inland is worth trying. A few cases I have sent to the higher altitudes in Switzerland have done well, but I can conceive nothing worse for a patient than one of the popular Swiss resorts in the month of August. Care, on the whole, is of far more importance than climate. The great point is to get the patients to a place where they can find peaceful quiet and rest, with freedom from noise and nuisances, where they can have real comfort and wholesome food, and where they can enjoy pure and bracing air among pleasant and cheerful surroundings. Sea voyages as a rule are prejudicial and can only be sanctioned when the patient is well on the road towards recovery, is a good sailor, and can travel in comfort.

Massage may prove beneficial in the case of patients who are confined to bed as well as in the case of those who are able to go about, but it must be judiciously employed. The hygiene of the skin should be carefully supervised on account of its increased action. When the patient is confined to bed, sponging of the whole body with tepid water twice a day is advantageous. In other cases a warm bath (98° to 100° F.) may be allowed every night. Warm sea-water or brine baths are sometimes useful; but bathing in the open sea is generally contra-indicated. Effervescent saline baths, which can be prepared at home with Sandow's tablets, seem sometimes to have a quieting influence on the heart. Local cold applications to the thyroid have sometimes been found to quiet the circulation. Cold compresses or Leiter's tubes may be conveniently used for this purpose.

The principal drugs which have been employed are those which have an effect on the heart or circulation, on the nervous system, or on the thyroid gland. Digitalis is well spoken of by some authorities, and may be given in the form of tincture or infusion, or, as some prefer, Nativelle's digitaline or digalen may be prescribed. I have never seen the administration of digitalis or strophanthus produce any slowing of the

heart's action in this disease, and some patients seem worse instead of better for it. Tincture of convallaria may be given in doses of 10 to 15 minims three times a day, and according to Prof. G. R. Murray it is more useful in controlling the pulse-rate than the two other drugs. Belladonna, in doses of 10 to 15 minims of the tincture three times a day, on the whole gives good results. It appears to sooth the nervous system and to diminish the excitability and restlessness; possibly by lessening the activity of the thyroid gland. However, it is not a drug which should be given continuously over a long period, and its administration should be suspended from time to time. I have found bromide of potassium of value when the nervous symptoms predominate; 20 to 40 grains may be given with benefit at bedtime to a restless, excitable, emotional subject who sleeps badly. Opium, which was recommended by Dr. Cheadle and others, has not proved beneficial in my experience. Preparations of iodine are sometimes useful in cases in which the goitre is large or in which it is increasing in size. Iodide of potassium, or preferably iodide of sodium, may be given in small doses, 3 to 5 grains, three times a day. The syrup of hydriodic acid, in doses of a fluid dram three times a day, is sometimes better borne than the iodides and seems as effective. Another form in which iodine may be given internally is iodipin, which is a stable compound of iodine and sesame oil and is prepared in two strengths, 25 per cent for external and 10 per cent for internal use. Iodipin (10 per cent) may be given internally in doses of $\frac{1}{2}$ to $\frac{1}{4}$ jij daily. Preparations of iodine may also be applied externally over the goitre. The tincture or liniment cannot be applied without staining the skin, and, if repeatedly used, causes some soreness. Iodipin (25 per cent) may be employed without these disadvantages. Half a dram should be gently rubbed into the skin over the thyroid daily. In some cases the iodine treatment is not well borne, and should it be found that the patient is not improving, is losing ground, or suffers from aggravation of the cardiac or nervous symptoms, the use of iodine, either internally or externally, should at once be discontinued. Iron is indicated when the disease is combined with chlorosis or anaemia, but not otherwise. Arsenic is sometimes beneficial, and 2 to 5 minims of Fowler's solution may be given after meals. 15 to 30 grains of phosphate of sodium may be given three times a day; it can be safely said that it does no harm, and in some cases I fancy that it has done good, although it is difficult to say why. Chloride of calcium has also been given with apparent benefit. Cod-liver oil or pancreatic emulsion may be given when there is malnutrition. Some recommend these in large doses, and by the rectum as well as by the mouth. Strychnine is indicated in cases in which the heart needs stimulation.

It is unnecessary to add that treatment should always be carried out on general principles and complications dealt with as they arise. If dyspepsia be present, or diarrhoea, or constipation, the appropriate remedies must be employed. In the cases with troublesome vomiting, citrate of potassium

in large doses, or bismuth may be given, but if it continues it is advisable to suspend feeding by the mouth and to administer nourishment for a time by the rectum.

Treatment by means of galvanism has long been employed. It was first introduced with the object of influencing the sympathetic in the neck, one pole being placed at the back of the neck and the other over the sympathetic, first on the one side, then on the other. It is recommended that weak currents should be used, and their direction should be reversed. One pole may be applied also to the eyes, the thyroid, and the region of the heart. Vigouroux prefers faradisation to galvanism. The positive pole of a large electrode is applied to the neck, while the negative, a small electrode, is applied in succession to the carotids, to the eyelids, and to the goitre. I have made a fair trial of both methods, and am very doubtful whether any benefit has followed their use apart from the mental impression made upon the patient.

I have recently made some trials of α -ray treatment which has been applied by Dr. Greg in the Electrical Department of St. Thomas's Hospital. This treatment has had a remarkable effect in reducing some cases of enlargement of spleen, and I hoped that a similar result might be obtained in the goitre of Graves' disease. But the results so far have proved disappointing.

Troussseau has recorded that great relief has been afforded during attacks of dyspnoea by leeching or bleeding.

Severe attacks of palpitation are sometimes relieved by the application of an ice-bag to the praecordium.

Of recent years thyroid, thymus, and other organic preparations have been employed. Thyroid gland preparations, theoretically speaking, should always make the disease worse. Although usually I have found the patient's symptoms distinctly aggravated even by small doses, yet in some cases I have given large doses without affecting the patient in any way. I have, however, seen benefit in certain cases, namely, in cases of old standing in which the symptoms seem to be due rather to deficient than to excessive secretion. The thyroid gland in these cases has usually been little enlarged. The cases with solid oedema which have already been referred to are nearly always benefited, and I have seen the swelling almost entirely disappear under the treatment. A number of cases of apparent benefit from thymus gland preparations having been reported by various observers, I made an extensive trial of thymus in 20 cases of the disease, and compared the results with those in 20 similar cases treated without thymus. The conclusion I came to was that no appreciable effect followed their administration, although in a few cases the patients felt better while taking them. Suprarenal gland has been thought to be beneficial by some physicians, and extract of spleen has also been tried. I believe I was the first to make use of the various animal glands in the treatment of Graves' disease; for in 1892, as soon as I had satisfied myself of the therapeutic effect of thyroid gland when given by the mouth in myxoedema, I gave it in full doses in

Graves' disease. I then tried pituitary body, cerebral tissue, orchitic extract, and thymus, but found them all more or less without effect.

In 1899, Otto Lanz treated patients with the fresh milk of thyroidectomised goats with decided benefit. The inherent difficulties in carrying out this treatment have prevented it from being more extensively put to the test. Mr. W. Edmunds, however, has recently treated 3 cases in this way, and in 1 case the improvement which followed the treatment was very decided. I am indebted to Mr. Edmunds for the following particulars. No licence is required to carry out a recognised treatment such as this. Goats take ether well and the operation can be performed while the goat is in kid or after she has kidded. In goats the thyroid consists of two separate lobes, one on each side, and there is no isthmus. One difficulty in carrying out the treatment is that very little goat's milk of any kind is to be had in the late autumn from October to December. The unpleasant taste which goat's milk sometimes possesses is probably due to what they are allowed to feed on, and if proper care be exercised with regard to their food their milk is not unpalatable. The method of Lanz has led to the production of a substance called rodagen; it is a powder prepared from the milk of thyroidectomised goats by a process elaborated by Burghart and Blumenthal, and is described as containing 50 per cent of the active constituent of the milk with 50 per cent of sugar of milk added to preserve it. From an extensive trial I have no doubt that in some cases it has decidedly benefited the patients who have taken it. Most of the patients say they feel better, sleep more soundly, and are less nervous while they are taking it. In some there has been a considerable gain of weight as the result of the remedy. Three of the cardinal features of the disease, the exophthalmos, the goitre, and the tachycardia, have usually remained unaltered, but even these in some cases have improved. The dose is generally described as 1 to 3 drams a day, but I believe that in severe cases considerably more should be given if benefit is to be obtained. The main drawback to giving large doses is the expense of the remedy. In severe cases I have given as much as an ounce a day, and it is only by giving large doses that I have been able to get good results. I have never seen any bad results from the administration of rodagen except that one of my patients thought it had a purgative action. Some patients object to the somewhat cheesy flavour of rodagen. An antithyroid serum, prepared by Merck from the blood of thyroidless sheep, has also been employed, and is also expensive, 10 c.c. costing about five shillings. I treated a number of patients with it, giving from 1 to 5 c.c. daily, and did not observe that it had any conspicuous therapeutic effect. It is possible that if I had given larger doses I might have observed more decided effects as in the case of rodagen. Doses as large as 5 c.c. three times a day have been given in cases in which benefit has been recorded.

Surgical Treatment.—Medical treatment, general or local, it must be admitted, is sometimes most disappointing. Where we are most in need

of help drugs are most likely to fail us. It is not surprising, therefore, that surgical methods of treatment have long been advocated and employed with the object of bringing about a more certain and speedier cure. If we could be certain that the essential and fundamental cause of the disease is the hypertrophy and over-activity of the thyroid gland the most rational method of treatment would obviously be to reduce the enlarged gland to something like normal proportions by surgical means. It is many years since partial thyroidectomy was first performed in Graves' disease. Lord Lister in 1877 removed the bulk of a goitre in a case of this disease in which life was threatened by suffocation. In a few weeks all the symptoms were alleviated, and the patient, who was still alive in 1887, then presented few signs of her former malady. Since that time larger or smaller portions of the goitre have been surgically removed in many cases, and a good many successful results have been published. Unfortunately, the operation has its own dangers, and these are greatest in the class of case which responds least to medical treatment. Allen Starr's statistics, published in 1896, shewed a considerable mortality as the result of operative measures ; out of 190 cases operated on, 23 died as the immediate result of the operation, 3 were in no way improved, 45 were improved, and 74 were reported as entirely cured ; in 45 the results were doubtful. The later statistics collected by Rehn embrace 291 thyroidectomies ; of these 165 were followed by cure, 77 by improvement, and 37 by death. The death-rate for the whole number was just over 12 per cent, but for the severe cases it was as high as 22 per cent. The mortality given by Rehn closely agrees with that recorded by Mayo and Schultze. It is pointed out by Rehn that whilst the results of ligature appear to be worse than those of excision, the explanation is that the more severe cases are submitted to ligature, the less severe to excision. We may compare these with Kocher's results obtained out of 106 cases ; these were : cured, 62, or 58·5 per cent ; greatly ameliorated, 9, or 8·5 per cent ; ameliorated, 17, or 16 per cent ; not traced, 9, or 8·5 per cent ; died, 9, or 8·5 per cent. Kocher's results are certainly better than those previously published, especially with regard to the lessened mortality ; but even in the hands of such a skilful surgeon the operation is still attended with considerable risk to life. Kocher states that ligature of one artery brings about a slight amelioration of the symptoms, ligature of two arteries produces a greater effect, ligature of three out of the four arteries may give a very good result, and still greater benefit follows excision of one lobe and ligature of the superior thyroid artery of the other side. Kocher admits that in all severe cases of Graves' disease there is much more reaction after operation than after excision of ordinary or even malignant goitres. There is a sudden rise of temperature and increased rapidity of the heart, the action of which may suddenly fail and death occur without warning. In two of my own cases death occurred within a few hours after the operation. One was a case with all the symptoms of disease present in a high degree, and in deciding on operation I was influenced by the absence of any improvement

on ordinary treatment during several months in the hospital. The other, however, was an incomplete case without exophthalmos, and operation was performed at the patient's own wish rather against than with my recommendation. Friedheim of Hamburg has recently reported observations on 20 cases treated by thyroidectomy, and says a lasting cure has been effected in 14, and in 5 others improvement has occurred; he thinks that the cases in which amelioration only occurred have still too much gland left behind. Thomas Huntingdon, in reviewing the detailed histories of a considerable number of cases resulting fatally within a short time after operation, says: "We cannot escape the conviction that general anaesthesia is in a very large proportion of them seriously at fault. There is no difference of opinion among operators as to the impropriety of general anaesthesia in this relation, and especially in advanced cases." Kocher recommends that the operation should be performed under local anaesthesia, being of opinion that a general anaesthetic adds greatly to the danger. In 3 cases in which he operated under general anaesthesia, thyroidism followed, 2 being fatal. I have no personal experience of operations on exophthalmic goitre performed under local anaesthesia, and in a recent visit to Switzerland I was informed that local anaesthesia is not much in vogue except with Kocher. Hartley, who has performed partial thyroidectomy in 15 cases, all under a general anaesthetic, does not consider a local anaesthetic preferable; one of his patients, however, died suddenly during operation. The other 14 were much benefited by the operation.

Were it not for the considerable risk to life from the operation, I should not hesitate to recommend it as the most rational and most practical method of treatment of the disease. In the milder forms there is, however, a good prospect of recovery under medical treatment, and there does not seem so much more to be gained by operation to warrant the incurring the risk of a fatal result. The risk of death from the operation is so high in acute and severe cases as to render it doubtfully justifiable, and few surgeons would be found willing to perform it. In several chronic cases in which the tumour has seriously interfered with the breathing, or in which other methods of treatment have failed, I have had partial thyroidectomy performed. In one, in which the exophthalmos was extreme, there was no improvement, whilst in others, in which the exophthalmos was slight or absent, decided improvement followed.

Another surgical method of treatment is resection of the cervical sympathetic. This, however, appears to be attended with as great risk to life as thyroidectomy. Although, according to Jaboulay, if the patient survives the operation good results follow, it is difficult to understand how this operation can exercise a curative effect.

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ACROMEGALY

By Prof. E. F. TREVELYAN, M.D., F.R.C.P.

ACROMEGALY, first adequately described and named by Pierre Marie in 1886 (19), is characterised by abnormal growth, especially of the hands, feet, and face; and is usually accompanied by more or less severe nervous symptoms.

Etiology.—*Age.*—Acromegaly usually begins in the third or less often in the fourth decade of life, but it has been seen before the fourth year (Moncorvo); on the other hand a few cases have begun after fifty.

Sex.—It appears to be more frequent in men than in women; in Hinsdale's 130 cases there were 73 males and 57 females.

Antecedent Conditions.—The onset of the disease is sometimes dated by women from the last childbirth; in a case under my care the disease was stated to follow the birth of a child thirteen years previously, two

children having been born since, and the menstrual function having ceased at the age of thirty-seven, only $3\frac{1}{2}$ years before she came under observation. Atrophy of the generative organs has been specially noticed by Freund. It is hardly surprising that acromegaly has followed some infectious diseases, such as influenza and enteric fever. In some instances injury has preceded the onset of the disease. Few authorities regard this as a definite cause, but Bleibtreu records a remarkable case in which the hypophysis cerebri was destroyed by a haemorrhage; the patient had a fall when sixteen years old, and at seventeen began to grow rapidly, shewed symptoms of acromegaly, and died of pulmonary tuberculosis at twenty-one. In connexion with heredity some exceptional but very striking observations have been recorded: both parents and child (de Cyon), father and son (Bonardi), father and daughter (Schwoner), mother and daughter (Emil Schaeffer) have suffered from acromegaly; the father had acromegaly, and the daughter congenital myxoedema (Pope and Clarke); the great-grandfather and aunt on the mother's side have shewn gigantism (Brissaud and Meige); Bregman noted partial giant-growth, namely a large thumb, in the sister and son of an acromegalic man who had the same peculiarity.

Morbid Anatomy.—The chief morbid changes are in the bones and cartilages, subcutaneous tissues, ductless glands, and not infrequently in the internal organs. The changes in the bones are largely hypertrophic; the periosteum may be considerably thickened and may form new bone, which is often irregular, so that thickening and irregularities are present, especially towards the epiphyses. Sometimes osteoporosis has been observed at the same time as the formation of new bone. There may be hypertrophy of the cartilages and also of the subcutaneous tissues. The organs, especially the heart, liver, and spleen, may be enlarged (splanchnomegaly), as was well seen in Ravaut's case. This visceral enlargement may be a true hypertrophy, or may be due to proliferation of the connective tissue. On the other hand, the generative organs have been found to be atrophied. By far the most important changes are found in the so-called ductless glands. It is universally admitted that in the overwhelming majority of cases of acromegaly the hypophysis cerebri is diseased; it may be the seat of a haemorrhage (Bleibtreu), hyperplasia, or of tumour or cyst formation. The tumour originates in the anterior or glandular lobe of the hypophysis, or invades it secondarily. Sarcoma, glioma, adenoma and other epithelial growths, and even tuberculous and syphilitic granulomas, have been known to occur in the hypophysis. The sella turcica may be widened and deepened by the tumour, which may penetrate deeply into the sphenoid and even appear in the nasal cavities, as in Strümpell's case, or make its way upwards through the diaphragm covering in the sella turcica, and project as a large mass into the cavity of the skull, as in a specimen in the museum of the Royal College of Surgeons (Neal and Shattock). The position of the hypophysis cerebri explains completely some of the important symptoms of acromegaly; when enlarged it may press on the under and median

surface of the optic chiasma and upon the tracts, and thus produce in turn temporal hemianopsia, optic atrophy, and blindness. The thyroid gland may be hypertrophied, atrophied, or more rarely unaltered. Less frequently the thymus is persistent. Morbid changes are occasionally present in the pancreas, and have been regarded as the cause of the diabetes which sometimes complicates acromegaly; but in one of Stadelmann's cases there was diabetes with a normal pancreas, and in another changes in the pancreas but no diabetes. Adenomas in the suprarenals have also been described.

Pathogeny.—P. Marie (22) was the first to associate acromegaly with disease of the hypophysis cerebri, and, from the frequency with which the hypophysis is diseased in acromegaly, no hypothesis of the pathogeny of the disease can be regarded as satisfactory unless it explains the part which the hypophysis plays in its production. Unfortunately there is little exact knowledge as to the function of this organ. It has been shewn experimentally that the hypophysis is necessary to life (Paulesco; Vassale and Sacchi); but it is not known how it influences the growth of tissues and organs, presuming that it does exert this action. The functional activity of the hypophysis might obviously be diminished or suppressed, increased, or altered; Marie suggested that suppression of the function of the hypophysis was the cause of acromegaly, but the objection to this view is that hyperplasia of the gland is not uncommonly present. According to Tamburini, acromegaly is due to excessive functional activity of the hypophysis cerebri, which induces hypertrophy, and is eventually followed by either atrophy or tumour formation. This hypothesis undoubtedly explains why symptoms of intracranial tumour are so frequently present, and the subsequent atrophy would account for the cachexia in the later stages of the disease. Benda, who supports this hypothesis, lays special stress on the presence of chromophil cells as evidence of hyperactivity, and points out that it may be difficult to distinguish between hyperplasia and sarcoma of the hypophysis. The objections to the hypothesis that disease of the pituitary is the exclusive cause of acromegaly are, (*a*) that a tumour may destroy the hypophysis without any sign of acromegaly, and (*b*) that acromegaly has been known to occur with a healthy hypophysis (Labadie-Lagrange and Degny, quoted by Modena). In reply to these objections it has been pointed out that a very exhaustive examination of the hypophysis must be made before it can be stated that the glandular structure has been completely destroyed (Burr and Riesman), that the pituitary tumour may not have been present sufficiently long to allow definite signs of acromegaly to appear, and that in elderly persons the function of the hypophysis cerebri may have ceased, so that destruction of the gland would not give rise to acromegaly (17). But these arguments, though ingenious, do not completely meet the objections.

The frequency with which the thyroid gland is affected in acromegaly, taken in conjunction with the enlargement of the hypophysis noted in myxoedema and after experimental thyroideectomy, has led observers

to believe that some interference with the normal interaction of these glands is responsible for acromegaly. Other writers believe that the other ductless glands play a part in the pathogeny of the disease.

The relation between acromegaly and gigantism must be close, as 20 per cent of acromegalic are giants and 40 per cent of giants develop acromegaly (Sternberg (40)); and necropsies on giants shew that enlargement of the hypophysis is nearly always present. Brissaud regards acromegaly as the gigantism of adult life, and gigantism as the acromegaly of the period of growth properly so-called. Sternberg (41), however, argues that gigantism is not necessarily pathological. Some look upon gigantism as only disposing to acromegaly, and a very few would regard their association as accidental.

Symptoms.—*The onset* of the disease is gradual. In women the first symptom is frequently the arrest of menstruation. Paraesthesiae commonly occur early. Gradually the hands, face, and feet become manifestly enlarged. Very exceptionally, as in Dr. Stevens's case, the symptoms of gross intracranial disease—namely, tumour—precede the more strictly acromegalic symptoms; whilst in rare instances symptoms of tumour are absent throughout the disease, as in Bleibtreu's case. The course of the disease is variable, but is usually slow; Sternberg (41) recognises three forms of the disease: (1) the benign, which may last as long as fifty years; (2) the chronic, lasting twenty years, and including most of the cases; and (3) the acute, with a duration of three or four years, and due to sarcoma. Death in acromegaly may result from a cachexia with deepening stupor, from cardiac asystole, or from coma, due to increasing intracranial pressure. Occasionally diabetes brings acromegaly to a rapid termination in coma, as in Ravaut's case, in which death occurred about 6½ months after the onset of diabetes. Intercurrent disease, such as pulmonary tuberculosis, is sometimes responsible for the fatal issue.

In its complete form the disease presents unmistakable features. The massive and long oval-shaped face is disfigured by a large nose, a markedly projecting lower jaw (prognathism), and often by greatly accentuated supraorbital ridges and prominent malar bones. The lower jaw may be so prominent that the upper row of teeth falls within or coincides with the lower. The intervals between the teeth are often widened. The lower lip is thick and unsightly, the tongue often much enlarged, and the palate, uvula, and tonsils may share in the hypertrophy. The voice may be low-pitched and rauous, from the increased cavity of the larynx consequent upon the enlargement of the laryngeal cartilages. Other cartilages, such as those of the ears and even the tarsal cartilages (de Silvestri), may increase in size. Usually there is an abundant growth of coarse hair. The hands are large and spade-like, and the movements of the sausage-shaped fingers are clumsy. Exceptionally the fingers may be elongated, as occurs in the slender as against the massive type of acromegaly (Marie (21)). The nails may be longitudinally ribbed, but this is not constant. The feet are affected in

a very similar way to the hands, and flat-foot is not uncommon. The long bones of the limbs are not usually altered, but in some instances their distal extremities share in the enlargement. An *x-ray* examination shews that the bones of the hands and feet are broadened. Occasionally irregularities and thickenings can be made out, especially towards the epiphyses. Sometimes the large size of the hands and feet may be chiefly, if not solely, due to hypertrophy of the soft parts. In the neck the thyroid gland may be enlarged or diminished. Both clavicles may be enlarged, and more rarely the hypertrophy affects the second ribs. The antero-posterior diameter of the thorax is increased as against the transverse. Erb drew attention to an impaired percussion note over the upper part of the sternum, which he attributed to a persistent and enlarged thymus, but it must be remembered that the sternum may be thickened, as in one of Stadelmann's cases. Kyphosis is very constantly met with in the cervico-dorsal region, with a corresponding lordosis of the lumbar spine.

There may be troublesome thirst, and a large quantity of urine may be passed; not very infrequently there is temporary or permanent glycosuria. Excessive sweating is common. There may be distressing paraesthesiae, consisting of tingling and numbness in the hands, less often in the feet, and occasionally definite pains in the legs, which have been attributed to the vascular disease shewn by Bonardi and others to occur in acromegaly. The nervous symptoms usually appear later, and are mainly those of gross intracranial disease, namely, headache, ocular disturbances, and less frequently vomiting. Headache is rarely absent, even in the earlier stages of the disease, and eye symptoms almost always appear as the disease advances, the defect in sight being often a temporal hemianopsia. Wernicke's hemiopic reaction may be present, as in Mr. Lynn Thomas's case (45). There may be inability to recognise colours, especially green, by the affected half of the retina, for some time before temporal hemianopsia in the usual sense is discovered. This hemianopsia may gradually pass on into blindness, first in one and then in the other eye; so that hemianopsia in one eye, and blindness in the other may precede bilateral blindness. Optic atrophy is common, but optic neuritis is somewhat rare. Exceptionally there is paralysis of the third nerve or of its branches, but the sixth nerve escapes. Occasionally exophthalmos is present, and the pulse-rate may then be permanently increased, as in Dr. Cattle's case, but hypertrophy of the bony boundaries of the orbit may, to some extent, obscure the exophthalmos. The mental symptoms in acromegaly, which have been studied by Farmarier, usually take the form of depression of the mental functions, including dementia, rather than exaltation, as in Pick's and Schlesinger's cases (34). The general mental state is usually one of heaviness, drowsiness, and hebetude. General weakness short of true paralysis is often noted in the advanced disease. Atrophy of muscles has been recorded in a few cases (Bregman), and the knee-jerks may disappear.

The associated diseases and complications of acromegaly include diabetes, exophthalmic goitre, myxoedema, cardiac and vascular phenomena. Lorand has paid special attention to the unusual but significant combination of either exophthalmic goitre or myxoedema with acromegaly; usually acromegaly supervenes on these diseases and not conversely. Some spinal cord diseases, such as tabes (Nonne) and syringomyelia, have been seen in combination with acromegaly; syringomyelia, however, may produce the enlargement of the extremities called cheiromegaly (Marie (20), Schlesinger (35)).

The diagnosis of the disease presents no great difficulty except in the earliest stages. The distribution of the hypertrophies suffices to distinguish it from leontiasis ossea and from Marie's pulmonary osteo-arthropathy (*vide* Vol. III. p. 64). For the distinction from myxoedema with which acromegaly was at one time confused, see p. 356. The peculiar eye symptoms make the diagnosis of an enlarged hypophysis producing pressure practically certain. Skiagraphy has been employed to disclose the enlarged sella turcica and the presence of a tumour (Oppenheim and others, quoted by Bruns (8)).

The prognosis of acromegaly is unfavourable. In the large majority of cases the disease is slowly but steadily progressive. In the benign cases it may last many years, and the usefulness of the patient may not be greatly impaired. In cases in which the symptoms of gross intracranial disease appear early, the prognosis is hopeless, because the tumour implicating the hypophysis is almost certainly malignant; but even these cases may take two or three years to run their course. Quite exceptionally a decided improvement has taken place in the eye symptoms (Schlesinger, Prodi).

The following methods of treatment have been tried : (1) *Hypophysis treatment* may give relief from the headache and paraesthesiae, as in a recent case under my care, and though this result is palliative only, its value must not be underestimated. (2) *Thyroid treatment* has been followed by improvement in some of the symptoms, notably in cases recorded by Bruns (7). (3) *Combined thyroid and hypophysis treatment* has been followed by relief in a few cases (Rolleston). (4) *Drugs*.—Arsenic and iodides have been employed with indifferent success, but antisyphilitic treatment has led to improvement in one or two cases. Antipyrin and other antineurals, such as exalgin, have been used to relieve pain. (5) *Surgical treatment*, by removal of the pituitary tumour, has been attempted, but the proof of its value has yet to be established. As a palliative measure trephining has been of service, as in Dr. Mitchell Stevens's case, in which the benefit was not limited to the relief of the headache, and in a less degree in Dr. Caton's case. In intractable headache trephining certainly deserves a trial.

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ADDISON'S DISEASE

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SYNOMYS.—*Morbus Addisonii*, *Melasma Addisonii*, *Bronzed disease*, *Asthénie surrenale*, *Mélanodermie asthénique*.

Definition.—An exaggeration of the normal pigmentation of the skin, associated with extreme prostration, muscular and cardiovascular asthenia, and a liability to syncope, nausea, and vomiting. After death the chief or only lesions are in the suprarenals.

History.—In searching for the cause of pernicious anaemia Thomas Addison of Guy's Hospital discovered the association between disease of the suprarenal bodies and the train of symptoms that bears his name. This observation was first reported publicly in a paper (6) read in 1849 before the South London Medical Society; but it attracted no attention until 1855, when Addison (5) published a monograph of thirty-

nine pages "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules." The discovery was slow to receive general recognition, and in the prefatory remarks appended to the reprint of this paper in Addison's collected writings, published by the New Sydenham Society in 1868, eight years after his death, it is stated that "even now it (Addison's disease) does not find a place in the nosology of some writers." To the loyal and unselfish efforts of Sir S. Wilks the general acceptation of this remarkable discovery is largely due; he collected, sifted, and described in the Guy's Hospital Reports the clinical features and pathological details of numerous cases of the disease. Trousseau gave honour to whom honour is due in naming the morbid entity Addison's disease. Greenhow, in the Croonian Lectures on Addison's disease before the College of Physicians in 1875, collected a large number of cases, and gave a very complete review of the subject, to which little was added for fifteen years. The great advance in our physiological knowledge of the ductless glands has led to corresponding interest and research in connexion with their diseases. This has resulted in considerable attention being paid to the pathology and treatment of Addison's disease.

Comparatively little has been added to our knowledge of the clinical aspect of the disease since it was first described by Addison. The nature of the lesions found and the mechanism by which they lead to the symptoms characteristic of the disease have, however, been interpreted in different lights.

Etiology.—The disease is rare; Dr. Tatham of the General Register Office kindly informs me that the number of deaths from "diseases of the suprarenal bodies" in England and Wales averages 172 annually (81 males and 91 females). He adds that almost all these deaths are from Addison's disease, because death from haemorrhage or malignant new growth of these bodies would be tabulated under the heading of haemorrhage or malignant new growth and not under that of the local disease; of 193 cases tabulated by Greenhow, 125 (or 65 per cent) were males and 68 (or 35 per cent) females, and Lewin found that 60 per cent of the cases were males and 40 per cent females, but Dr. Tatham's official figures shew that it is rather commoner in women.

It occurs on an average at about thirty-one years of age, and is extremely rare late in life; whilst only a very few examples in infants have been recorded; Dezirot has collected 48 cases in children under 16 years of age.

It does not seem to be proved that the disease is more frequently seen in tuberculous families, or that it is in any way hereditary. Cases in two brothers have been recorded (Andrewes, Schwab); I have knowledge of cases in two sisters, and the disease has been described in mother and four children (Fleming and Miller).

Tuberculous disease of the suprarenals may be associated with tuberculosis elsewhere in the body, especially in the lungs; in children Addison's disease, when it occurs, is said to be commonly associated with

tuberculous mesenteric glands. The adrenals may become infected, by a process of extension, from tuberculous osteitis of the lumbar vertebrae; Alexais and Arnaud were able to refer to twenty-three cases of this association of morbid changes. On the other hand, the suprarenals are often the sole site of tuberculosis in the body. Strains or injuries to the back and blows on the abdomen have seemed to be the cause of the disease; this may be explained by supposing that the injury so impaired the vitality of the organs as to render them vulnerable to the tubercle bacilli: or, again, trauma may have given rise to haemorrhage into the substance of the suprarenal capsules; the destruction of the glands, and the subsequent fibrosis, leading to Addison's disease (Borrmann). Suprarenal haemorrhages, probably traumatic, were found in 25 out of 105 still-born children examined by Dr. Spencer. Dr. Wainwright has recorded the case of a child aged two months, in whom the organs shewed changes probably due to extravasation of blood into their substance. It is therefore possible that, in some instances, Addison's disease may be the result of extensive damage received from the extravasation of blood into their substance during birth; the slighter cases probably end in recovery, or no signs of the disease appear.

Greenhow was of opinion that Addison's disease was more rarely seen among the upper ranks of society than among the labouring classes, who are more exposed to injury. It must be remembered, however, that it is far from being a common disease; and that if its incidence in the labouring and leisured classes were proportionately equal we should see many more cases among the former.

Morbid Anatomy.—*Condition of the Suprarenal Capsules in Addison's Disease.*—In Addison's monograph 11 cases are recorded; in five of these cases there was caseous tubercle in both suprarenals, and in one case (No. 9) tubercle was present in one suprarenal, but this may have been a case of generalised melanosis secondary to a primary growth of the uveal tract. One case (No. 4) appears to have been an example of fibrosis and atrophy. In three cases there were secondary carcinomatous growths in the suprarenals; bilateral in one case, unilateral in the other two. In one additional case there was a secondary nodule of carcinoma blocking the right suprarenal vein and associated with haemorrhage into the corresponding gland, but there were no growths in either.

Addison took a broad view of the relation of the symptoms to the morbid lesions, and expressed himself to the effect that any morbid lesion of the suprarenals may produce the same result, and that the result depends not so much on the nature of the organic change as upon the interruption of some special function of those organs. Subsequently, Addison appears to have been inclined to modify his views in respect of the multiplicity of morbid conditions of the suprarenals and the uniformity of the series of symptoms, and to have desired to remove from among the cases in his monograph those of malignant disease of the suprarenals. With regard to the cause of the symptoms, he conjectured that the intimate connexion of the suprarenal bodies with the sympathetic

was largely concerned in their production ; thus, in some degree throwing over his original opinion that the interruption of some special function of the suprarenals was the explanation of the characteristic features of the disease. According to Sir S. Wilks (*Guy's Hospital Reports*, 1862), Addison in a discussion at the Royal Medical and Chirurgical Society expressed himself as follows :—" We know that these organs (the suprarenals) are situated in the direct vicinity and in contact with the solar plexus and semilunar ganglia, and receive from them a large supply of nerves, and who can tell what influence the contact of these diseased organs might have on these great nerve centres, and what share that secondary effect might have on the general health and in the production of the symptoms presented ? "

Sir S. Wilks taught, and with no uncertain voice, that all genuine cases of Addison's disease are due to one and the same lesion of the suprarenal bodies. This view might be called the unity of Addison's disease. The lesion would now be considered to be tuberculous, but Sir S. Wilks considered it to be a primary inflammation comparable to hepatic cirrhosis, and regarded the atrophied cirrhotic condition of adrenals sometimes seen as the last stage of the fibro-caseous change.

Greenhow, as a follower of the doctrine of the unity of Addison's disease, criticised severely all the recorded cases in which the morbid condition of the suprarenal bodies was other than the fibro-caseous change ; and concluded either that the symptoms (especially the pigmentation) were not characteristic of Addison's disease, or that the lesion found was incorrectly described.

The conditions of the suprarenals recorded in cases of Addison's disease are the following :—

- (i.) The fibro-caseous lesion due to tuberculosis—far the commonest condition found.
- (ii.) Simple atrophy, sometimes so extreme that the organs cannot be found after death.
- (iii.) Chronic interstitial inflammation leading to atrophy.
- (iv.) Malignant disease invading the capsules, including Addison's case of a malignant nodule compressing the suprarenal vein.
- (v.) Blood extravasated into the suprarenal bodies.
- (vi.) No lesion of the suprarenal bodies themselves, but lesions, pressure, or inflammation implicating the semilunar ganglia and sympathetic.

The first is the only common cause of Addison's disease. The others, with the exception of simple atrophy, may be considered as very rare.

(i.) The fibro-caseous or tuberculous change in the suprarenals begins in the medulla. It has been said to start in the cortex, but this must be exceptional, and care must be taken not to regard as small tuberculous masses the adenomas frequently present on the surface of the cortex. Miliary tubercles, at first scattered in the substance of the medulla, increase in size, and, by coalescing, gradually take the place of the whole or varying amounts of the organs, which thus become enlarged—

weighing several times the normal amount—nodular, and deformed. After destroying the cortex this morbid process readily sets up inflammation in the contiguous tissues, and is the cause of adhesions to the surrounding organs. When it is of old standing, fibrous tissue is developed around the caseous or mortar-like tuberculous masses, which from calcareous infiltration may become cretaceous. On the other hand, the caseous material may soften down so as to form an abscess in the enlarged suprarenals. Tubercl bacilli have been found very frequently; but repeated and careful examinations may fail to demonstrate their presence. Prof. Delépine inoculated caseous material from the suprarenals of a case of Addison's disease into guinea-pigs, but no tuberculosis resulted. From this it may be concluded that, although the lesion is generally tuberculous, it is not necessarily so in all cases, or at least cannot be proved to be so.

Generally the lesion is present, though often in different stages, on both sides; but since its discoverer's time, cases of well-marked Addison's disease have been found associated with a unilateral lesion.

The fibro-caseous change is the one usually met with in Addison's disease. In 287 cases collected by Lewin it was present in 211. As in the lungs so in the suprarenal bodies, the tuberculous is more frequently seen than any other form of chronic inflammation. Tuberculous change in the suprarenal bodies is frequently found without any signs or symptoms of Addison's disease, present or past. Such cases should not be described as "Addison's disease without any symptoms"; for the affection is a clinical and not a pathological concept. Of 131 cases in which death was chiefly or directly due to tuberculosis this was the case in 18. In 11 the lesion was unilateral, bilateral in the remainder. In contrasting the comparative liability of the suprarenal bodies to tuberculosis with the marked immunity of the thyroid gland it is noteworthy that the physiological actions of their respective extracts are opposed.

(ii.) Well-established examples of simple atrophy of the suprarenal capsules, without any fibrous increase in the substance of the organ, or of any fibrous adhesions around them, have often been described as giving rise to the clinical picture of Addison's disease. In 1903 Simmonds collected 26 cases of this kind. The atrophy in some of the cases was extreme, the organs in many cases requiring very careful dissection. In some instances they are described as being of the size of peas. It cannot be wondered at that in some cases they were stated to be absent. These cases are of great importance, as will be seen later, in supporting the conception that the symptoms of the disease are due to the absence of the functional activity of the organs, and not to irritation of the neighbouring important sympathetic nerves. In these cases of atrophy the sympathetic plexuses and semilunar ganglia were in most instances carefully examined, and stated to be normal.

(iii.) Chronic interstitial inflammation of the suprarenals, leading to atrophy, has given rise to typical Addison's disease. The fibrosis is quite

unconnected with the production of any caseous material, and does not shew any evidence of tubercle, such as bacilli. It has, however, been suggested that toxins absorbed from tuberculous foci elsewhere may act on the adrenals and produce fibrosis. Haddon compared this change in the suprarenals to that in the thyroid gland in myxoedema, and endorsed Addison's original opinion that the essential factor in Addison's disease is, as in myxoedema, a destructive change, the anatomical condition being of no consequence as long as it is destructive.

(iv.) Malignant disease of the suprarenal capsules occasionally gives rise to some of the symptoms of Addison's disease; such as gastric disturbance, extreme debility, and pigmentation. Characteristic cases of Addison's disease are naturally those in which there is no other organ affected, and in which the disease runs its own course without any complications. When secondary growths arise in the suprarenals the primary growth may give rise to symptoms which throw into the shade or obscure any that may be due to interference with the suprarenal bodies. The comparatively rapid progress of the primary malignant disease may kill the patient before the secondary affection of the suprarenal bodies has had time to lead to any distinct symptoms. Again, in many cases the presence of malignant disease, if ascertained, would be quite sufficient to explain any symptoms which otherwise might be due to suprarenal disease. Still, from Addison's time downwards, examples of secondary malignant growths in the suprarenal capsules associated with the symptoms, especially with the pigmentation, of Addison's disease have been recorded; and it is to be borne in mind, therefore, that new growth in the suprarenals may produce symptoms comparable to those met with in definite cases of Addison's disease. It is undoubtedly true that the suprarenals may apparently be almost completely destroyed by carcinoma, and yet no special symptoms result. The same, however, is true of tuberculosis, and especially when there is extensive tuberculous disease elsewhere. Perhaps in both cases death occurs before symptoms characteristic of Addison's disease have had time to develop, or there may have been sufficient chromophil cells in accessory adrenals or in connexion with the sympathetic to keep up a supply of adrenalin.

In primary malignant disease of the suprarenal bodies there seems little evidence that the symptoms of Addison's disease occur. It has been thought that this is because the cells of the growth carry on the functional activities of the normal organ.

(v.) A few cases have been recorded, shewing an apparent connexion between haemorrhages into the suprarenals and blood-cysts occupying them, on the one hand, and the symptoms of Addison's disease on the other.

(vi.) Definite lesions of the suprarenals are present in about 88 per cent of the cases of Addison's disease (Lewin). Apart from disease of the suprarenals of the various kinds already mentioned, there are cases in which symptoms like those met with in Addison's disease are found in association with alteration of the semilunar ganglia or abdominal

sympathetic, the suprarenals appearing healthy. Thus, the solar plexus and semilunar ganglia have been surrounded by lymphadenomatous growths, whilst the suprarenals were found to be intact. In such instances there must be considerable interference with the vascular connexions of the suprarenals, more especially with the thin-walled veins and lymphatics.

Condition of the Adjacent Sympathetic, etc.—The condition of the semilunar ganglia and sympathetic plexuses has been the subject of much attention. They have been found invaded by the inflammatory process, sclerosed, and degenerated. Greenhow described (*a*) a stage of irritation of the semilunar ganglia and the nerves connecting them with the suprarenals, as shewn by redness and swelling; and (*b*) a further stage of atrophy and fatty degeneration.

On the other hand, the absence of any alteration of these same structures has been repeatedly recorded. Thus, 49 cases of Addison's disease due to tuberculous disease of the suprarenal bodies, in all of which the condition of the sympathetic was specially examined, were collected from various sources by Alexais and Arnaud. In at least 12—that is, 24 per cent—of these cases the nervous structures were described as normal. An intimate knowledge of the normal anatomy of the parts is of great importance. The extremely careful examinations made by Dr. Robinson for Dr. Mann on two cases of Addison's disease serve as a model for such investigations; since a control examination was made at the same time of the same structures from a patient of the same age in whom there was no reason to suspect anything abnormal. Von Kahlden described hyaline degeneration and thickening of the vessel walls, small-celled infiltration, perivascular haemorrhages, and pigmentary atrophy of the ganglion cells and thickening of their capsules. These changes were regarded as having a direct causal relation to the symptoms of Addison's disease. He found the splanchnic nerves in the two cases quite healthy. Jürgens and Fleiner, however, have described degeneration of the splanchnics in Addison's disease. The bearing of these observations must be considered in the light of variations described in the normal histology of the semilunar ganglia in adults (80). The cells may be pigmented and atrophied, the degree of atrophy increasing with age; the fibrous tissue is often increased in amount, and there may be small-celled infiltration without any apparent reason. The condition of the semilunar ganglia and of the adjacent sympathetic being so inconstant in cases of this disease, the changes described in them have no satisfactory claim to be considered as causal factors in the production of the disease.

Changes in the central nervous system have been described in a few cases only, and, if they had any relation at all to the disease, were the result rather than the cause of the morbid state. A softened condition of the brain, with an increased amount of cerebrospinal fluid, has been recorded in some cases of Addison's disease, and was probably accidental; Hyperaemia, small-celled infiltration, and degeneration of nerve fibres and cells have also been recorded in isolated cases, but though their

occurrence is of interest from the marked inflammatory changes resulting from removal of the suprarenals in animals by Tizzoni, no importance can be attached to them. In connexion with the view that Addison's disease is of the nature of a toxæmia, it would be natural to expect to find changes corresponding to those in the spinal cord in pernicious anaemia. Neuritis of the posterior root ganglion and sclerosis of the cord have been described in some cases, but further observations are required.

Other Anatomical Lesions.—Hypertrophy of the lymphoid follicles of the stomach and intestines, enlargement and softening of the spleen, and persistence of the thymus may occur. The heart is usually atrophied and often weighs considerably under the normal.

Pigmentation of the peritoneum has been recorded in a few isolated instances, but is probably the result of inflammation, and not therefore of any special importance. Similar change is not met with in other serous membranes. Pigmentation of the pia mater (36) has once been observed ; but here again it may possibly have been due to some accidental or concomitant cause, such as malarial melanaæmia.

Anatomical Distribution of the Cutaneous Pigment in Addison's Disease.—The pigment is generally regarded as melanin and the same as that normally present in the skin except as to quantity. Melanin is formed by the cells in the stratum Malpighii and is not derived directly from blood pigment. Microscopically the pigment is found in the cells of the stratum Malpighii, the more superficial layers of the epidermis being quite or almost free from any pigment. The dermis shews a few pigmented cells, "carrier cells," which have been thought to convey the pigment from the blood-vessels of the dermis to the stratum Malpighii. These wandering cells are found around the vessels in the superficial parts of the dermis.

Situation of the Pigment in the Buccal Mucosa.—Divergent opinions have been expressed on this point ; Greenhow and Brault regard the anatomical position of the pigment as identical with that in the skin ; and this was confirmed as regards the pigmentation produced experimentally in the buccal mucosa of rabbits by Tizzoni. On the other hand Haddon found the pigment quite as plentiful in the corium as in the stratum mucosum of the buccal mucous membrane. Dr. Dixon Mann draws a sharp distinction between pigmentation of the mucous membrane and that of the skin. In mucous membranes the pigment has a different histological site ; the corium contains pigmented carrier-cells, as is the case in the skin, but the stratum mucosum contains no pigment ; when, exceptionally, pigment was found in the stratum mucosum, it was seen to be not in but between the cells. Pigmentation of mucous membranes is not general ; it requires certain local conditions (friction, local hyperæmia) for its development.

The mechanism by which the pigmentation is produced has been variously explained. The notion that it was due to the deposition of effete blood pigment, retained in the circulation from incapacity of the adrenals to deal with it, has been abandoned for want of proof. It is generally

assumed that the pigmentation is an exaggeration of the normal and the result of over-activity of the cells of the stratum Malpighii due to increased nervous stimulation. It has usually been thought that there is mechanical irritation of the nerves around the adrenals by inflammation and adhesions, but this explanation breaks down for cases of pigmentation in which the adrenals are atrophied and pericapsular inflammation and adhesions absent. The stimulus to increased formation of pigment might quite reasonably be thought to be a toxæmic state of the blood, due in some way, as yet not understood, to failure of the functional activity of the adrenals. A toxæmic state might be conceived to stimulate either the sympathetic nerves or the pigment-producing cells directly. The existence of special nerves influencing pigmentation, through their action on cells like chromatoblasts, has not yet been proved.

The physiology of the suprarenals must be briefly considered before dealing with the pathology of Addison's disease. Brown-Séquard shewed in 1858 that the suprarenals are necessary to life, and that after complete removal of both the glands animals die rapidly with symptoms in some degree comparable to those of Addison's disease. When removal does not lead to this result, as was stated by a number of subsequent observers (Philipeaux, Harley, Tizzoni), it has either been incomplete or compensation has been effected by accessory suprarenals which undergo hypertrophy. Brown-Séquard's experiments have been often repeated and fully confirmed. Removal of the suprarenals was stated to be followed by a toxic condition of the blood, which Abelous and Langlois compared to that produced by curare, and regarded as the result of failure of an excretory or antitoxic function of the suprarenals; but it has been urged by Prof. Schäfer, that probably in any animal dying slowly the blood becomes toxic, and that this is not a specific effect of ablation of the adrenals. The results of removal were at one time regarded as due to damage to the adjacent sympathetic and not to removal of the glands, but this has been disproved. Further, after many attempts, it has been shewn that an animal can survive successive removal of the suprarenals one after the other, provided the first be grafted into the kidney and allowed to become established before the other is removed; subsequent removal of the graft is followed by death (Busch and van Bergen). A few observers have found that pigmentation follows experimental removal of the adrenals (Tizzoni).

The suprarenals are composed of (1) the cortex derived from the coelomic epithelium in the Wolffian ridge, and closely related to the sexual glands; and (2) the medulla derived from the sympathetic, and neuro-ectodermal in origin. The physiology of these two distinct parts of the organ will be considered separately. The cortex is larger than the medulla and is composed of epithelial cells, the structure of which suggests a high degree of functional activity; removal of the cortex, the medulla being left intact, has been followed by death of the animals, and some observers have concluded that Addison's disease is due to disease of the cortex. In spite of these considerations, which suggest that the

cortex has important functions and is essential to life, our knowledge as to its exact function is still very imperfect. Arguments can be adduced in favour of the following views:—(i.) that the cortex is intimately related to growth and development, especially of the sexual organs; the adrenals of animals have been noted to enlarge during periods of sexual activity and pregnancy, and a resemblance has been pointed out between the cells of the cortex and those of the corpus luteum. Hyperplasia of the cortex and especially cortical hypernephromas have been noted to be associated with precocious development of the sexual organs, hair, and fat in children (*vide p. 432*); whilst, conversely, hypoplasia of the adrenals has been observed in monsters and in some cases of retarded sexual development. (ii.) That the cortex has the power of neutralising poisons; hyperplasia of the cortex has been found in cases of renal disease with high blood-pressure and has followed the production of experimental lesions of the kidneys (Darré); these data suggest that the suprarenal cortex neutralises poisons due to renal inadequacy. Ciuffo's recent experiments point to the presence in the blood of animals deprived of the suprarenals of a body which prevents the toxic effects of adrenalin on healthy animals. These experiments, which require confirmation, suggest that the converse may also hold good. Myers shewed that cobra venom after admixture with an emulsion of suprarenal cortex was no longer toxic, control experiments with emulsions of the suprarenal medulla and of other organs being negative. But as these and a few other isolated data constitute most of the evidence in favour of the anti-toxic function of the cortex there is not enough proof of its existence. The suggestion that the cortex excretes effete blood-pigment or poisons has not been supported by any proof. (iii.) That the cortex is in some way concerned with the internal secretion of the medulla. Although it does not contain any pressor substance, it is conceivable that the cortex plays an essential part in the early stages of the formation of adrenalin, and that the process of elaboration is completed in the medulla, in which part alone the full activity of the secretion is acquired. In favour of this hypothesis Prof. Schäfer and Mr. Herring point out the analogy between the pituitary and the suprarenal glands. In both, the glandular epithelial parts (anterior lobe and cortex) are inactive, whilst the neuro-ectodermal parts (infundibular portion and medulla) yield a highly active extract. The close anatomical relation of the epithelial and neuro-ectodermal parts in the two glands suggests that their physiological relation may be equally close. It has also been suggested that the cells of the cortex secrete lecithin for use by the muscles (Bernard (10)).

The medulla contains cells staining a green colour with ferric chloride (Vulpian's reaction) and a brown colour with chromic acid, and are hence spoken of as chromaffin or chromophil cells. The pressor or vaso-constrictor substance contained in the medulla is produced by these cells, and it has been shewn that the function of the medulla is to produce an internal secretion which raises the blood-pressure (62) by acting on the terminals of the sympathetic; this substance was isolated by Abel in

1897 as epinephrin hydrate with the formula $C_{10}H_{13}NO_3 \frac{1}{2}H_2O$, and in 1901 by Takamine as adrenalin $C_{10}H_{15}NO_3$. It has been prepared synthetically (Dakin). The extremely active vaso-constrictor effect of adrenalin has led to its extensive use in various branches of surgery. There appears to be some antagonism between the action of adrenalin and that of curare, as an injection of adrenalin delays or diminishes the effect of curare (Panella). It has further been shewn that these adrenalin-producing or chromaffin cells are not confined to the medulla of the adrenal, but are found elsewhere in contact with the sympathetic, especially in the collections known as Zuckerkandl's parasympathetic bodies, the intercarotid and coccygeal glands; the medulla of the suprarenal thus forms the most conspicuous part, but not the whole, of what has been called the hypertensive system. This discovery is very important, as it explains why Addison's disease does not invariably follow destruction of the suprarenals by morbid changes.

PATHOLOGY.—The association between the morbid lesions in the adrenals and the characteristic symptoms of Addison's disease has given rise to much discussion and several hypotheses have been put forward.

The Nervous Hypothesis of Addison's Disease.—The early experimental work of Philipeaux, Harley, and, more recently, of Tizzoni, pointed to the absence or unimportance of any function on the part of the suprarenals. On such a basis the connexion between disease of the suprarenals and Addison's disease was explained by the secondary morbid changes, induced by the lesions of the suprarenals, in the neighbouring semilunar ganglia, solar plexus, and sympathetic nerves. This conception was based on the post-mortem evidence that inflammation spread from the tuberculous suprarenals to the semilunar ganglia and the sympathetic. Greenhow inferred that at least all the more important features and prominent symptoms of the disease were due to morbid changes in the nerves, the changes in the nerves being first of the nature of irritation and later of atrophy. The collapse and the extreme state of debility were thus explained as the result of the altered condition of the sympathetic in the abdomen. The vomiting and pigmentation were referred to the direct irritation of the sympathetic by the caseous material in the suprarenals, or to the same cause acting reflexly through the cerebrospinal system. The view of Sir S. Wilks and Greenhow may be summarised thus:—The lesion is primary in the suprarenals, and always of the same nature; and the symptoms of the disease are due to the secondary effect on the adjacent sympathetic, the solar plexus, and the semilunar ganglia.

A natural modification of these views is that Addison's disease is due to changes in the abdominal ganglia and sympathetic, which may be due to disease of the suprarenal bodies, but are independent of a special, or indeed of any lesion in them. This was supported by Jaccoud, von Kahlden, and others, from the clinical and morbid anatomy points of view, and by the experimental researches of Tizzoni. It has even been suggested that the irritation of and subsequent changes in the ganglion

cells and sympathetic fibres in the fibrous capsule of the suprarenals give rise to the symptoms of Addison's disease (Alexais and Arnaud). In this way the nervous conception of Addison's disease can be upheld even in cases in which the semilunar ganglia and abdominal sympathetic are found not to have undergone any abnormal change. The comparative rarity of these ganglion cells in the capsule of the organ renders this view unlikely, and in any case it would not explain the symptoms when the capsules are merely atrophied. The unimportance of the part played by the suprarenal bodies themselves was carried to an extreme by Semmola; he believed that not only had changes in the suprarenals nothing to do with Addison's disease, but also that when they did exist, they were trophic lesions due to disease of the nerves which presided over their nutrition.

The nervous conception does not explain the numerous cases recorded of typical Addison's disease, in which special attention has been paid to the condition of the semilunar ganglia and adjacent sympathetic, and in which they have been found to be normal; since continued irritation could not last for any time without setting up local inflammatory changes. Still less does it explain the occurrence of the symptoms of Addison's disease associated with simple atrophy of the adrenal bodies.

Conversely, there are numerous examples of slow irritation of the abdominal sympathetic by enlarged glands, spinal caries, "surgical" and tuberculous kidney, abdominal aneurysm, and chronic peritonitis, in which no symptoms of Addison's disease appear, except, perhaps, some pigmentation. Experimental section of all the nervous connexions of the suprarenal body does not give rise to the symptoms, produced either by its removal or by ligature of its efferent vein (Thiroloix), which are somewhat analogous to those of Addison's disease in man. These results do not support the view that Addison's disease is due simply and solely to an irritating and destructive lesion of the sympathetic around the suprarenals. It thus appears that this nervous explanation is untenable, at any rate in an exclusive sense.

The Hypothesis of Suprarenal Inadequacy.—If the purely nervous hypothesis of Addison's disease cannot be reconciled with the facts, attention must be directed to Addison's first and original view, that the symptoms of the disease are due to interference with the functional activity of the suprarenal bodies, or in other words, that Addison's disease is the outcome of suprarenal inadequacy. Before considering this question further it will be well to clear the ground by inquiring whether the facts of morbid anatomy are consistent with the hypothesis that Addison's disease is due to impairment or loss of function of the suprarenals.

Bearings of Morbid Anatomy on the Hypothesis of Adrenal Inadequacy.—It is known that destructive tuberculous lesions and atrophy of the suprarenal bodies may give rise to the symptoms of Addison's disease.

But the following objections may be raised to the conception of suprarenal inadequacy :—

(a) The existence of cases in which after death the suprarenals are found to be extensively destroyed by tuberculosis or new growth, and in which, nevertheless, definite clinical symptoms of Addison's disease have been absent during life. (b) That there are cases, clinically of Addison's disease, in which caseation of comparatively small amount is found in the suprarenals after death—perhaps only in one, and in which the amount of damage is even less than in cases which have presented no sign of Addison's disease. Since a comparatively small part of the available suprarenal substance is thus rendered functionless, it has been argued that the concomitant symptoms cannot be due to abolition of the function of the organs. And (c), lastly, that there are examples of Addison's disease in which the suprarenal capsules themselves are healthy, though the surrounding sympathetic nerve plexuses and semilunar ganglia are implicated in dense adhesions or in a growth, such as lymphadenoma.

In reply to these objections the following considerations may be brought forward :—

(a) In cases in which the organs are extensively destroyed by tuberculosis, or invaded by new growth, the absence of symptoms may be explained in two ways: (i.) the change in the adrenals is generally a secondary result of advanced disease in other organs, which kills the patient before the symptoms of Addison's disease, usually a chronic affection, have time to develop. (ii.) That some compensation for the destruction of the suprarenals is present in accessory suprarenals, or in the amount of chromaffin cells elsewhere in connexion with the sympathetic, and that symptoms due to the destruction of the main glands are thus avoided.

(b) In reply to the objection that when the lesion of the suprarenal substance is not of considerable amount the remaining part of the organ, if healthy, should produce compensation, and thus prevent the development of symptoms, it may be urged that failure in this power of compensation may be due to inherent want of vitality, to concomitant atrophy of the chromaffin cells in the gland and elsewhere, or possibly—and this is a point requiring investigation—to an interference with the efferent vessels by the tuberculous growth. The common tuberculous caseous change always begins in the medulla, and thus might easily obstruct the vascular and lymphatic connexions of the organ, and so render it impotent, even though a sufficiency of secreting gland tissue were left.

(c) In the few cases of Addison's disease in which the suprarenals are described as healthy, while the sympathetic and semilunar ganglia were involved in dense adhesions or in a growth, it is possible that the vessels and lymphatics of the suprarenal capsules were interfered with, and that the organs were thus practically placed outside the circulation and rendered functionless. The sequence of events, then, may be compared to Boinet's experimental ligation of the pedicle (and veins) of the suprarenal bodies, with its resulting fatal toxic effects. Hence it may be concluded that obstruction to the efferent vessels of the suprarenal capsules is a possible cause of Addison's disease. The facts of morbid

anatomy, then, appear to be compatible with the view that Addison's disease can be explained by suprarenal inadequacy.

If it be admitted that Addison's disease is the outcome of adrenal inadequacy, the further question arises whether it is (*a*) an auto-intoxication due to the deficient excretory or antitoxic activity of the suprarenal capsules, or (*b*) the result of an inadequate internal secretion of adrenalin.

A. *That Addison's Disease is an Auto-intoxication due to Inadequate Excretory or Antitoxic Activity of the Suprarenal Bodies.*—Of this first alternative there is no proof. Dr. MacMunn (45) believed that, normally, haemoglobin and histohaematin become changed into haemochromogen in the suprarenal bodies. Haemochromogen, according to him, is blood pigment in an excretory stage and is found also in the bile. He holds that in Addison's disease the failure of this function of the suprarenal bodies is shewn by the presence of a pigment—urohaematoporphyrin—in the urine. This body, which MacMunn also found in various other conditions, has been shewn not to be a definite chemical body, but to be a mixture of a larger quantity of haematoporphyrin and a smaller quantity of urobilin (24), both of which are among the normal urinary pigments. It has also been shewn that the urinary pigments are not increased in Addison's disease, and that haematoporphyrin may be present as a trace only (25). It is highly improbable, therefore, that the suprarenal bodies have any action on the effete blood-pigments.

What evidence is there that the suprarenals remove toxic substances from the circulation and then destroy them? Abelous and Langlois find that if the suprarenals are removed from an animal the blood becomes toxic to other animals of the same species, the suprarenals of which have been removed, the transfused animals dying sooner than they otherwise would. This poison Abelous and Langlois compared to curare. Blood from a few control animals, dying from other causes, did not appear to possess this toxic effect; but more observations are required as to the question whether the blood of dying animals is toxic or atoxic. It is conceivable that this toxæmic condition was the result of a suspension of the excretion of poisonous bodies, due to removal of the suprarenal capsules. But Tizzoni and Nothnagel crushed the suprarenals, and left them to be absorbed without any resulting signs of toxæmia; so that, at any rate, the suprarenal bodies do not contain the poisonous substances which they might be supposed to remove. This same hypothesis is further opposed by the experiments of Abelous and Langlois, who shewed that the toxæmia due to ablation of the organs can be counteracted by injection of suprarenal extract. Now, if the suprarenal bodies excrete a poison which, when accumulating in the blood, gives rise to toxic symptoms, injection of suprarenal extract should increase these toxic effects. These two observations, then, are both opposed to the hypothesis that the suprarenals excrete a poisonous substance.

The view that the suprarenals antagonise toxic substances in the circulation is attractive, but, as has been already pointed out, it has not been established. This point will be referred to again in connexion with

the hypothesis that Addison's disease is due partly to absence of adrenalin and partly to failure of the cortex to exert an antitoxic influence ; but it may be stated here that there is no satisfactory evidence that Addison's disease is due solely to failure of an antitoxic function exerted by the adrenals.

B. *That Addison's Disease is due to an Inadequate Supply of Adrenalin.*—Our knowledge that adrenalin is secreted by the medulla of the suprarenal glands and by chromaffin cells elsewhere, the low blood-pressure in Addison's disease, and the absence of adrenalin from the glands in fatal cases have made it clear that Addison's disease is due, in part at least, to absence of adrenalin or inadequacy of the chromaffin cells in the suprarenal medulla and possibly elsewhere ; this may be considered certain. We are not yet in a position to say that Addison's disease is due solely to deficiency in adrenalin ; the failure of adrenalin to cure the disease suggests that some other factor is present ; and the pigmentation, vomiting, and the occasional occurrence of terminal convulsions, point rather to some positive irritation, toxæmic or mechanical, than to mere absence of a normal stimulus.

It is also conceivable that Addison's disease is due to total adrenal inadequacy, suppression of the medullary secretion of adrenalin being responsible for muscular and circulatory asthenia, and suppression of the hypothetical antitoxic function of the cortex leading to a toxæmia which, by stimulating the sympathetic, induces excessive pigmentation. As has already been pointed out, the attractive hypothesis that the cortex of the suprarenal has an antitoxic function has yet to be proved, and until our knowledge on this point is more certain it is useless to discuss the question whether auto-intoxication due to this factor plays a part in the pathogenesis of Addison's disease.

Similarly, there is no proof that the mere absence of the tonic effect of adrenalin, by upsetting metabolism, induces a toxæmia. We are as yet far from a full understanding of the method of action of internal secretions. The secretion of the suprarenal bodies, by its interaction with other glands, might produce the equilibrium we know as health. Absence, deficiency, or perversion of the suprarenal secretion appears to lead to a profound disturbance of normal processes in the body. This disturbance might easily lead to the production or accumulation of poisons in the system—in other words, to an auto-intoxication. If Addison's disease is an auto-intoxication the urine should contain the toxic material, since the kidneys are practically always healthy. Here a sufficient amount of evidence is unfortunately wanting. Prof. Schäfer and Dr. Oliver have found that extracts from the urine of patients suffering from Addison's disease have the same effect as normal urine. Gioffredi and Tinno have found the toxic coefficient of the urine increased, but this was in a case in which there was in addition caseous tuberculous pneumonia ; so that no real importance can be attached to this observation. Neurine has been said to be present in the urine, and the phenomena of the disease have been referred to its action (48). This

statement especially is in need of more general confirmation. Mühlmann has put forward the view that the symptoms of Addison's disease are due to chronic poisoning with pyrocatechin. More extended observations are required on this subject, and until they are forthcoming judgment must be suspended. That Addison's disease is an auto-intoxication is no doubt an attractive supposition, but as yet there is but little positive evidence to support it.

The hypothesis that Addison's disease is due partly to absence of adrenalin, partly to nervous irritation, has been suggested by Dr. Byrom Bramwell (16), Neusser, and Boinet; this explanation combines the "nervous" and "inadequacy" hypotheses, and in the present state of our knowledge is difficult to controvert.

To sum up. Addison's disease is due to inadequacy of the chromaffin or adrenalin-secreting cells which are chiefly situated in the medulla of the gland, but are also found in connexion with the sympathetic trunks. It is possible that there is a second factor at work, namely, irritation of the sympathetic nerves, which might be (1) mechanical and due to adhesions and invasion of the pericapsular nerves and ganglia, or (2) toxæmic and due either to failure of a hypothetical antitoxic function of the cortex of the adrenals, or to disturbed metabolism resulting from absence of adrenalin.

Onset.—The onset of the disease is generally insidious and not marked by any special symptoms or features. The patient has been gradually losing energy and strength for a considerable time before seeking medical advice, which he does perhaps chiefly for the relief of gastric symptoms. Pigmentation may occasionally precede the manifestations of constitutional symptoms, and so be the first thing to be noticed; but the constitutional symptoms of general debility and gastro-intestinal irritability usually precede it.

In a few cases the rapid occurrence of severe symptoms may suggest a sudden onset; it is probable, however, that this is rather a well-marked advance or exacerbation in the course of this insidious disease than absolutely its first manifestations. The apparently acute onset of Addison's disease has been known to follow some sudden shock or depressing circumstance, and has been put down to the administration of a severe purge or to distress or worry.

Symptoms.—*Pigmentation*, which most often arouses the suspicion of the disease, is variable both in the time of its appearance and in its degree. Usually it follows the constitutional symptoms, and it may only occur shortly before the fatal termination, and be then but slightly marked or even entirely absent. In some infrequent instances the pigmentation appears to precede any subjective symptoms by years. In a case of Munro's, quoted by Greenhow, there was an interval of seven years between the appearance of pigmentation and the onset of constitutional symptoms. In some cases it is so marked as to resemble that seen in the dark races; such cases are, however, rare: more often it resembles the bronzing of sunburn, or the dirty sallow tint so frequently

seen in association with dyspepsia : the patient himself is often quite unaware of its presence. It may attract little notice even on the part of the patient's friends, who are generally the first to observe it ; or it may be put down by them to exposure, or to insufficient attention to personal cleanliness. The pigmentation is an exaggeration of the normal ; it has, generally speaking, the same regional and anatomical distribution, and is subject to the same influences, being increased by any local irritant applied to the skin. Hilton Fagge thought it probable that it would be absent in a patient kept in the dark. This experiment, so far as I know, has not been intentionally tested ; but the light to which patients are exposed may very well play a part in determining pigmentation at an early or a late stage of the disease. It would be interesting to know whether Addison's disease has ever been observed in an albino. The probabilities are against the concurrence of two such rare conditions ; but, theoretically, there should be no pigmentation in such a case.

Pigmentation is sometimes almost universal, but is usually partial, and is then first noticed on the face, neck, and the backs of the hands and fingers ; especially over the joints, where it throws into relief the nails, which appear remarkably white : in this last point the pigmentation of Addison's disease differs from that of the dark races, which it otherwise closely resembles.

The tint of the face is of very varying intensity, and contrasts with the teeth and with the sclerotics, which usually appear somewhat anaemic. In rare instances foci of intense pigmentation have been described on the conjunctiva (Leva), but this occurs in ochronosis and in phenolism and it is probable that most of these cases were really of this nature. The staining of the neck and face, like that seen occasionally in pregnant women, may shew considerable irregularity in its degree. There may be darkening of the hair during the progress of the disease, but according to Sir S. Wilks (79), the colour of the hairy scalp is not altered ; and the same is true of the skin where it is covered by the beard, etc., and of the eyelids. The lips, along the line where they come in contact, sometimes shew pigmentation ; and similarly, as the result of irritation most commonly due to carious teeth, the cheeks, the gums, or the tongue may become pigmented. Pigmentation of mucous surfaces is often absent, and, though it is generally regarded as a sign of considerable value, it is probable that the factor of local irritation is a powerful one in its causation. Should pigmentation of the mucous membrane of the mouth be found without any source of irritation, it may perhaps be regarded as an exaggeration of some trace of the condition seen in Lascars, in blue-gummed Negroes, and exceptionally, in healthy persons (54). The tongue may shew purplish inky stains near the free border, stains so arranged as to suggest contact with the teeth as a causal factor.

Passing from the exposed parts of the body, the pigmentation is found on the dorsal surface of the forearms and on the anterior folds of the axillae ; these, it should be remembered, are apt normally to be pigmented. The areolae around the nipples usually shew a marked alteration in tint,

comparable to that seen in pregnancy ; but I have on several occasions noticed that the pigmentation of the nipples is not so much increased as would have been expected from the change in the colour of the skin elsewhere. The lower part of the linea alba may belie its name, and become a dingy or brown streak. The genitals, perineum, and groins are darkened in tint, sometimes to a marked degree, and the mucous membrane of the glans penis, the labia minora, and vagina may present changes similar to those seen in the mouth. The dark areas pass by a gradual transition into the paler parts of the skin. If, however, any part of the cutaneous surface have been irritated, as for example by a blister, the resulting increase in pigmentation has a comparatively sharp definition. The combination of Addison's disease and leucoderma has often been described, but the diagnosis in many of these cases is open to question. Parts of the body which are exposed to friction or pressure shew an increased pigmentation in an especial degree. Thus, the waist where it is compressed by corset or belt, the knee where the garters are tied, the shoulders under the braces, or the prominent vertebral spines present a darker hue. The palms of the hands and the soles of the feet, which are subject to as much if not more pressure than other parts, are very rarely pigmented, but I have twice seen pigmentation of the palms with intensification along the various lines. The tissue of scars remains unaffected, but the surrounding skin shews an exaggeration of pigmentation. Dr. B. Bramwell has reported a case in which the pock-marks of small-pox were pigmented. Greenhow attached considerable diagnostic value to the presence of small, well-defined specks, like small moles, on already discoloured parts of the skin. It may, however, be questioned whether these spots can be considered pathognomonic of the disease.

Generally speaking, pigmentation, though suggesting the disease, is not of itself, apart from constitutional symptoms, sufficient to warrant a positive diagnosis.

A white line on the skin of the abdomen after mechanical irritation, the converse of the familiar tache cérébrale, was described by Sergent as a sign of suprarenal inadequacy and low blood-pressure ; Bernard's observations shew that this sign is inconstant and of no value (9).

Asthenia.—This is perhaps the most frequent and important of the constitutional symptoms. At first the patient is easily tired, never feels rested, even after a long night, and gradually becomes more and more indisposed for any exertion, however slight, whether of body or mind. As the disease advances, life becomes a burden, but the sufferer has not even sufficient vitality to complain of its weight. Impotence is seldom referred to in the reported cases, but is probably not infrequently present. The muscular feebleness is not accompanied by any corresponding emaciation ; there are no signs of peripheral neuritis. This condition of invincible languor has been compared to that brought about by the action of a poison like curare in a minor degree. Langlois (36) lays stress on the total loss of sustained muscular effort which distinguishes Addison's disease from phthisis and other causes of great debility. In

fact, in cases of doubtful diagnosis he recommends recourse to Mosso's ergograph.

Symptoms referable to the Vascular System.—The want of muscular tone and contractility is not limited to the voluntary muscles. The systole of the heart is greatly enfeebled, as is shewn by the small, extremely soft and compressible pulse which, in some cases, may even become imperceptible at the wrist. The arterial blood-pressure is extremely low ; the maximum systolic pressure may fall to 60-65 mm. of mercury in the later stages, especially shortly before death. Janeway and Dr. G. A. Gibson, however, quote cases in which the blood-pressure was not low. In a case under my care the pressure rose from 80 to 100 mm. Hg as the result of treatment with adrenalin.

The temperature is generally subnormal and the extremities cold, so that the patient's state has been compared to that of chronic collapse. The depressed state of the circulation is further seen in a liability to syncope ; especially when the patient's head is raised. There is considerable danger that one of these fainting fits may prove fatal. Cardiac weakness is also sometimes shewn by palpitation and distressed breathing on movement. Sighing and yawning are sometimes present. An offensive or cadaveric smell is occasionally noticed to emanate from the patient.

Although the temperature is usually below normal this is by no means universal ; there may be fever, especially shortly before death, from some acute infection.

Addison, probably because he discovered this disease when looking for the cause of pernicious anaemia, considered anaemia as one of the chief symptoms. The recorded blood-counts shew some variation ; usually the red blood-corpuscles are diminished to about 2,500,000, but in some instances counts of 6,000,000 or even more have been recorded ; it is possible that this is the result of concentration of the blood due to vomiting. It is true that the contrast of the bronzed skin with the sclerotics, which are usually pearly, may give the impression of anaemia. But though anaemia and Addison's disease may coincide, they are not specially, much less inseparably, connected.

The subjects of Addison's disease retain about as much subcutaneous fat as they had before the onset of the disease. They may be thin or spare and lose weight, but they do not become remarkably emaciated.

Gastro-intestinal Symptoms.—The tongue is usually clean and moist, but the appetite is poor and may be capricious. The loss of the healthy desire for food is an early symptom, and accompanies the insidious onset of general debility and loss of tone. In the later stages this indifference may pass into positive loathing. The hydrochloric acid in the gastric juice may be diminished or absent. Nausea and retching are generally met with. Vomiting may occur throughout the course of the illness, but "is rarely absent in advanced stages, and may be spontaneous, and so irrepressible as to cause death from exhaustion" (Greenhow). Persistent hiccup may be a troublesome feature. The bowels are usually confined, but severe attacks of diarrhoea may supervene, and are sometimes so

uncontrollable as to carry the patient off. The constipation is but one more manifestation of the general loss of muscular tone already referred to. In exceptional cases acute abdominal symptoms imitating appendicitis or even peritonitis may come on (Ebstein, Nattan-Larrier).

Nervous Symptoms.—The general loss of vitality is shewn by the depressed functional activity of the nervous system. The acuity of vision may be impaired, flashes of light may pass before the eyes, and the perception of auditory sensations is sometimes dulled. There is in rare cases a feeling of intense irritation which prevents sleep. The mental processes remain clear to the end, or until a final coma or delirium supervene. In such a condition of unconsciousness signs of irritation of the nervous system may shew themselves in muscular twitchings or rigidity, or even in general convulsions. Headache and vertigo are by no means rare, and are most often associated with faintness. Pain is sometimes complained of in the limbs, and is often present in the loins, epigastrium, or hypochondriac regions. The extension of inflammation from the adrenal bodies to the neighbouring organs and tissues is probably responsible for much of the lumbar pain. The knee-jerks are usually diminished and may be absent.

Urine.—There are no constant or characteristic features in the urine. It is usually normal, or slightly diminished in amount, though there may be polyuria. Shortly before death the amount of urine may be very considerably diminished, and suppression has been recorded. Albumin and sugar are absent, in the later stages there may be a trace of albumin. As a result of intestinal disturbance indican may be present in the urine, but is not of any further significance. Excessive urobilinuria may occur, but is not constant. The observations of Thudichum and Dixon Mann shew that there is a diminution rather than an increase of the urinary pigments. Cordone described a pigment in the urine of cases of Addison's disease with the same characters as the melanin of the skin and of melanotic sarcoma. The excretion of urea, uric acid, and ammonia has been found to be normal. Neurine has been described in the urine by some observers who believe the disease is due to an intoxication set up by this body, but this requires further confirmation.

Course of the Disease.—The course of the disease is not uniform, and though progressive is not regularly so, even in the same individual. As in pernicious anaemia, there are exacerbations or paroxysms, during which all the symptoms become accentuated. After each of these crises the patient rallies, but is generally left in a worse position than before. Dr. Greenhow laid stress on these alternate exacerbations and remissions, and pointed out that the pigmentation follows the same lines, being exaggerated together with the symptoms; and that, though it diminished during the succeeding remission, it still remained more marked than it was before the last attack.

Usually the constitutional symptoms are the earliest to appear and the more prominent throughout.

Cases may prove fatal without any pigmentation; in these examples

of Addison's disease without bronzing the symptoms usually run a rapid course. On the other hand, the pigmentation is occasionally the first, and for a varying time the only manifestation of disease. Sometimes one of the constitutional symptoms is more especially noticeable, sometimes another; thus there may be a tendency to vomiting and diarrhoea, the disease presenting a gastro-intestinal character; or fainting fits and extreme breathlessness on movement constitute what may be called a cardiac type. But all the while there is intense and increasing asthenia.

Duration.—The period over which symptoms referable to the disease occur is very variable. The onset is generally extremely gradual and the progress may be very slow; cases, indeed, have been recorded in which the duration appeared to be as long as seven or even ten years. After death the changes in the suprarenal capsules are as a rule of old standing—caseous or cretaceous tubercle. Whether after the development of definite symptoms the course of the disease can become arrested, and be considered cured, is a difficult question. The extremely prolonged course of some cases might well suggest that the morbid lesion had become arrested, and a certain degree of compensation effected; and that a recrudescence of tubercle, analogous to that often met with in the lungs, or some acute infection, was responsible for the finally fatal issue.

There is no doubt that considerable destruction of the suprarenals by tuberculosis is not infrequently met with in persons who have died from other causes, and in some of them the early symptoms of the disease may at some period, perhaps long antecedent to death, have been present, though possibly not sufficiently prominent to arrest attention. In any case of apparent recovery the difficulty of diagnosis and the possibility of the disease being latent must always be taken into consideration.

Be this as it may, the duration in the great majority of instances is long. The average length of time, in a number of cases collected by Sir S. Wilks, during which symptoms were present, was eighteen months. This calculation, however, included the rarer instances in which the disease runs an apparently acute course. In the latter the lesion has been progressing, as seen at the autopsy, for months or even years, but no prominent symptoms had been manifested, and the disease has been spoken of as being latent. Suddenly, perhaps from some acute infection, the symptoms burst out in full force, and the patient dies in a few days or weeks. Between the very chronic and these remarkably acute cases there are intermediate grades which will be found to contain most of the cases met with in practice. It has been suggested that cases with simple atrophy of the adrenals run a longer course than those with tuberculous adrenals (13).

Termination.—Death may be quiet and gradual from asthenia, the patient being conscious to the last; or a "typhoid" or semi-comatose condition may precede it. Not infrequently sudden syncope extinguishes the flickering flame of life; severe attacks of vomiting or diarrhoea may so exhaust the already debilitated patient as to be the immediate cause of death. Sometimes delirium, muscular twitching, or general

convulsions may precede death. Death, however, may occur long before the patient becomes bedridden, as in an instance recorded by Prof. Osler (53) of a physician who had hardly completed his arrangements for retiring from practice when he died from sudden syncope. Death may be so sudden that the patient is not known to have been ill.

Prognosis.—The disease when sufficiently advanced to warrant a positive diagnosis is probably always fatal. It must be admitted, however, that diagnosis in an early stage is not only difficult but uncertain. Its recognition by its features, when well marked, is much like the diagnosis of malignant disease by the cachexia, in which case it is equally true that the prognosis is hopeless.

Arrest may sometimes occur after initial symptoms of slight intensity have shewn themselves; thus, cases of cure have been reported after the administration of suprarenal gland substance (*vide p. 419*). In 293 cases collected by Lewin, before this form of treatment came into vogue, 10 cases are recorded as being cured, and 25 as having shewn improvement. The existence of Addison's disease makes the prognosis very bad in the event of any acute infectious disease. The occurrence of pregnancy in the subject of Addison's disease makes the prognosis extremely grave.

Diagnosis.—The diagnosis of Addison's disease is by no means easy; we may suspect it, but to go farther and give a dogmatic opinion is often somewhat hazardous, and not warranted by the facts at our disposal.

Advanced and well-marked cases may be recognised at once; but the disease in its early stages, or cases in which either the pigmentation or the constitutional symptoms are absent or ill developed, may be regarded as the evidence of trivial ill-health, or biliousness, or as merely accidental. Conversely, minor ailments, especially the protean manifestations of dyspepsia, may simulate it. Although Addison's disease is sometimes revealed only on the post-mortem table, and this is especially so when the course is rapid and pigmentation is absent, it is probable on the whole, perhaps from the interest attaching to this comparatively rare affection, that it is more often diagnosed than proved to exist.

The diagnosis is rather one of exclusion, especially of abdominal disease, some forms of which may produce a passable imitation both of the pigmentation and of the constitutional symptoms of Addison's disease.

Since pigmentation is the most objective sign, and therefore the one which most frequently arouses a suspicion of Addison's disease, it will be well to consider first those conditions of pigmentation which may be mistaken for the melasma Addisonii. Chronic tuberculous peritonitis and malignant disease of the peritoneum, without apparently interfering with the functional activity of the suprarenal bodies, may be accompanied by considerable pigmentation of the face. The rare condition described as acanthosis nigricans may supervene in cases of malignant disease within the abdomen. This pigmentation of the skin is most marked on the face, in the axillae and groins; it differs from Addison's disease in that the skin is thickened and shews an exaggeration of its normal folds. Acanthosis nigricans has been thought to be caused by

pressure on the sympathetic. In some cases of malignant abdominal disease there may be compression of the vessels and lymphatics of the organ, which is tantamount to rendering them functionless. The condition then is one of Addison's disease. A similar result has been met with occasionally in lymphadenoma implicating the glands around the suprarenals. More rarely disease of the stomach, such as dilatation or chronic ulcer, may bring about darkening of the skin. It has also been noted in the recurrent vomiting of childhood (Shaw and Tribe). In haemochromatosis the pigmentation closely resembles that of Addison's disease, but the liver and spleen are usually enlarged and in late stages there is glycosuria from fibrosis of the pancreas (*diabète bronzé*). The after-effects of jaundice must be borne in mind in the diagnosis. In former days jaundice appears to have been not infrequently confounded with the discolouration of Addison's disease. In some cases of hypertrophic biliary cirrhosis, especially the juvenile form (*vide p. 192*), there is a distinct brown coloration of the skin; this has also been described in "family cholaemia" (Gilbert and Lereboullet). Examination of the conjunctivae and of the urine should at once settle any doubt. In chronic renal disease with granular kidneys the face sometimes presents a ginger-bread colour. The rare condition of ochronosis, in which the cartilages are blackened, has been mistaken for Addison's disease (56). Pregnancy and uterine irritation in certain cases lead to very noticeable pigmentation of a somewhat patchy character. In chronic pulmonary tuberculosis pigmentation may be very considerable; Boinet speaks of this condition as Addisonism (*vide p. 423*); it may very closely resemble that of Addison's disease. Malarial melanaemia produces a general darkening of the skin, and in melanotic sarcoma notable pigmentation of the skin, quite apart from the presence of growths, has been noticed (Legg); in fact Addison's ninth case in his original Memoir appears to have been of this nature. According to Wagner, the histological position of the pigment in the skin in such cases of melanotic sarcoma is the same as in Addison's disease. Carbone considers that the presence of sulphur in the pigments of Addison's disease and of melanotic sarcoma distinguishes them from that resulting from the destruction of red blood-corpuscles such as occurs in the melanaemia of malaria.

In exophthalmic goitre the skin may become so pigmented as to give rise to a diagnosis of Addison's disease combined with Graves' disease. Recovery in such a case may give rise to the erroneous impression that Addison's disease has been cured. In rare instances cutaneous pigmentation accompanies scleroderma. In von Recklinghausen's disease the pigmentation is associated with neurofibromatosis, and it has been suggested, but on insufficient grounds, that the cutaneous pigmentation is due to suprarenal inadequacy.

In rheumatoid arthritis not only a darkening of the skin but the appearance of black freckles also may be noted. Occasionally in this disease a well-marked collar of pigment is seen on the neck.

Argyria is rare, but this discolouration, which follows on the absorption

of silver salts and their subsequent deposit in the skin, is very striking. It is permanent, and has resulted from the medicinal use of nitrate of silver internally for gastric ulcer or tabes, or from its external application to sores. In argyria the distribution of the pigment and the colour of the skin are not the same as in Addison's disease. The exposed parts of the skin are chiefly affected, the silver is deposited between and not in the cells, and the colour is first grey and subsequently blue.

The medicinal use of arsenic if persisted in, for example in chorea and grave anaemias, may lead to a cutaneous pigmentation which may have much the same distribution as that of Addison's disease. In the epidemic of arsenical poisoning among beer-drinkers in Manchester and the neighbourhood in 1900, a number of cases were from the marked pigmentation first diagnosed as Addison's disease. It appears that pigmentation of the mucous membrane of the mouth is never seen in arsenical poisoning.

Long-continued irritation of the skin and the accompanying hyperaemia may result in a general discolouration which has been confused with that of Addison's disease. Greenhow laid stress on that seen in "elderly persons of very indigent circumstances and uncleanly habits, especially when infested with vermin," or "vagabond's disease."

In syphilis, also, the skin may become discoloured, and some cases of Addison's disease that have improved under a course of iodide of potassium may have been of this nature.

The distribution of tinea versicolor should prevent any confusion between it and melasma Addisonii. In pellagra the skin may be darkened, and the dyspepsia, pains, and early paralytic symptoms might simulate those of Addison's disease; pellagra, however, is an endemic disease not met with in England (*vide* article "Pellagra," Vol. II. Part I. p. 892).

Lastly, the darkening of skin due to hereditary influences, exposure to the sun, or to tar, or to the heat of furnaces in gas-works, must not be regarded as evidence of suprarenal disease. Addison's disease in blacks would be a matter of very great difficulty. Dr. Seheult has recorded a case in a negress, Dr. W. S. Thayer has kindly given me the details of a negro who probably had the disease, and Beaven Rake described Addison's disease in a syphilitic Hindoo, who was also the subject of leprosy. In cases of pigmentation of doubtful nature the effect of the administration of adrenalin on the blood-pressure may be determined; it is said that in healthy persons there is no alteration, whilst in incipient or definite Addison's disease there is a rise of 10 mm. of mercury as determined by the sphygmomanometer (O. Grünbaum); but this is not pathognomonic, for in a woman under my care with pigmentation and debility a rise of blood-pressure of 15 mm. of mercury and great improvement in the general symptoms followed the administration of adrenalin; she went out of the hospital, but died soon afterwards, and the autopsy, so Dr. F. M. Turner informed me, shewed carcinoma of the oesophagus and healthy adrenals.

Addison's disease without pigmentation can only be diagnosed after the elimination of any other satisfactory cause. Gastric disorders, especially some cases of carcinoma, leading to vomiting and asthenia, may resemble Addison's disease without pigmentation. Myasthenia gravis should be recognised by the myasthenic reaction. Pernicious anaemia does not present the facies of Addison's disease, and in any case of doubt its characteristic blood changes would settle the question. The early stages of splenic anaemia might, from the occasional presence of pigmentation, suggest Addison's disease; but on examining the abdomen the splenic enlargement would be detected at once and would thus prevent any mistake. The debility and sickness in those exceptional instances of Bright's disease, with a low blood-pressure, would be accompanied by oedema and albuminuria. In doubtful cases the tuberculin test, estimation of the opsonic index, and Calmette's ophthalmic reaction may be employed; as the adrenal lesion in Addison's disease is usually tuberculous, a positive result is in favour of this diagnosis.

Treatment.—The treatment naturally falls into two categories:—

(1) The special form of treatment by suprarenal gland substance in various preparations. An attempt is thus made to combat the results of suprarenal inadequacy; and (2) the symptomatic treatment on general principles.

Suprarenal gland substance and its active principle have been given in various forms by the mouth or hypodermically. Since the active principle, adrenalin, is rapidly oxidised by the tissues the use of hypodermic injections would appear to be contra-indicated; it is said that subcutaneous injection does not raise the blood-pressure, but that intra-muscular injection does (Brooks and Kaplan). Repeated intravenous injection is impracticable, and is not entirely free from danger. As it has been shewn that the activity of suprarenal extract is not in any way impaired by contact with pepsin and hydrochloric acid, this method, which in other ways is the easiest, has been mainly employed. It should be mentioned, however, that Swale Vincent has failed to get any toxic effects in animals by giving suprarenal glands and their extracts by the mouth, and concludes that the active principle is not absorbed when taken into the stomach. It is known that adrenalin inhibits absorption, and it is probable that the passage of adrenalin into the circulation is slow, that it is stowed away in the muscles, and does not influence the blood-pressure of healthy subjects. In patients with adrenal insufficiency or with Addison's disease, however, a rise of blood-pressure appears to follow administration of suprarenal extract or adrenalin by the mouth.

The suprarenal glands have been given in a natural state, in the form of a watery or glycerin extract, as a tincture, as a dry extract in the form of a pill or tablet, and as solutions of the active principle known as epinephrin, suprarenin, adrenalin, or adrenin (Schäfer (60)). The dosage is still a little uncertain; 15 grains of the gland substance three times a day has often been the initial dose, and has been increased up

to 2 drams of the gland substance in the twenty-four hours; larger amounts have been given. A solution of adrenalin chloride, 1 in 1000, physiologically standardised, is a convenient preparation; at first 10 minims of this solution in water may be given three times a day; the effect on the blood-pressure and the general condition must be watched and the dose may be gradually increased. The treatment should be persisted in for long periods, but the patient should be under medical supervision, as bad effects have been ascribed to suprarenal medication, though there is room for doubt as to the correctness of this interpretation. Since adrenalin produces arterial lesions when given to animals in large doses, the question arises whether it ever has this effect when given in Addison's disease. In a case in point in which adrenalin given hypodermically had produced a rise of blood-pressure, Loeper and Crouzon found old atheroma with acute change engrafted upon it; in a woman who had received 2000 intra-muscular injections of adrenalin for asthma the aorta shewed focal necroses (Brooks and Kaplan). Other bad effects, especially oedema of the lung, have been ascribed to the use of adrenalin; but, generally speaking, the quantity given to human beings is not sufficient to produce the effects seen experimentally in animals.

The effects of suprarenal treatment are, it must be admitted, very disappointing and bear no comparison with those of thyroid medication in myxoedema. Sometimes there is no effect; often there is temporary improvement, but a relapse occurs although the treatment is continued; in some cases the improvement leads to interruption of the treatment, and a relapse and increase of pigmentation follow. The temporary improvement has been explained as due to suggestion or to the coincidence with the periods of amelioration sometimes seen in the course of chronic cases. In some cases long-continued improvement or even a cure has been reported; cases of cure require very critical examination, since doubt as to the correct diagnosis must arise. Differences in results may depend on variations in the activity of the preparations used, and on the stage of the disease—early or advanced. Further, the result of treatment may possibly depend on the nature of the morbid changes present in the suprarenal bodies, namely, whether there is simple atrophy or tuberculous change with implication of the adjacent sympathetic, for the best results would naturally be anticipated from the use of adrenalin in cases of uncomplicated suprarenal inadequacy due to atrophy of the medulla of the glands. Dr. Adams impartially analysed 105 cases of Addison's disease treated with suprarenal gland substance in one form or another, and divided the cases into four groups: (a) in which alarming or fatal results were ascribed to the treatment—7 cases; (b) in which no benefit accrued from the treatment—49 cases; (c) in which marked improvement coincided with the treatment—33 cases; and (d) in which permanent benefit (?cure) apparently resulted from the treatment—16 cases. Thus, in more than half the cases no benefit at all resulted, but he concludes that this means is more likely to do good than any other kind of treatment. With this I agree, but some writers consider

this form of treatment quite useless. Dr. Batty Shaw concludes that unless grafting of the suprarenals be made practicable, which is not the case at present, there is little or no hope of curing Addison's disease by organotherapy.

In a case of Addison's disease under my care Dr. Golla produced a rise of blood-pressure by injecting subcutaneously a solution of the pressor substance of the pituitary gland; but this form of treatment has not been employed sufficiently to justify any conclusion as to its value.

General Lines of Treatment.—When there is marked muscular weakness and debility the patient will naturally keep in bed; but even apart from this the slightest tendency to syncope should be regarded as an urgent indication for perfect rest in the horizontal position. Death has occurred from this cause long before asthenia had become a prominent feature. Great care should in such cases be exercised in raising the head. During an exacerbation of the symptoms, and for some time after, the patient should be kept in bed. Worry, over-exertion, exposure to cold, and all danger of exhausting the patient's feeble strength, should be vigilantly guarded against. Open-air treatment has been followed by good results and by a gain in weight (B. Bramwell (17)), but cold must be guarded against. When improvement has taken place a quiet life should still be enjoined.

A simple, easily digested, and nutritious diet should be provided, and constipation warded off on the one hand, and diarrhoea on the other.

Strong purgatives should be avoided, from the danger of syncope resulting from shock after their use; in a case of Addison's disease previously latent the administration of a purge led to a fatal issue (Greenhow). Diarrhoea should be restrained by opium, bismuth, or other appropriate remedies.

Vomiting may be almost uncontrollable, and may rapidly bring about a fatal termination. Ice, fluid food in small quantities frequently repeated, effervescing draughts, soda water, and champagne may be given to combat it. As drugs, oxalate of cerium, bismuth, morphine, and opium should be tried. Hydrocyanic acid may act as a cardiac depressant. Grawitz has obtained good results by washing out the stomach, feeding through the oesophageal tube, and giving hydrochloric acid.

Tonics such as strychnine, arsenic, or iron, if there be anaemia, may be given; and if the stomach will tolerate it, some palatable combination of cod-liver oil and maltine should be tried. For the cardiac weakness and low blood-pressure digitalis may be given.

Oestreich has recorded a case in which surgical removal of a tuberculous suprarenal body was followed by disappearance of symptoms resembling those of Addison's disease. Before the operation a mass regarded as enlarged glands was felt close to the spine and was thought to be the cause of the symptoms. If the symptoms were due to the tuberculous adrenal they must have been the result purely of irritation of the sympathetic and not in any way due to suprarenal inadequacy.

In ordinary cases of Addison's disease operation is entirely out of the question, as the shock would almost certainly prove fatal.

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OTHER DISEASES OF THE SUPRARENALS

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IN the preceding article on Addison's disease reference has been made, incidentally, to many morbid conditions of the suprarenal bodies. Although certain of these changes do not necessarily give rise to symptoms, it is desirable, nevertheless, to include a general account of them.

Atrophy.—The organs vary considerably in size, but they are relatively larger in early life. They share in the general growth of the body, and as old age approaches participate in its involution. Extreme atrophy of the adrenals has already been referred to as a cause of Addison's disease (*vide p. 399*). Hypoplasia, or imperfect development, of the glands has been found in monsters, especially with cerebral defects, and in some cases of retarded sexual development; it has also been tentatively suggested as the cause of the *status lymphaticus* and haemophilia (Wiesel). Atrophy presumably means suprarenal inadequacy.

Suprarenal Inadequacy.—This is perhaps the best place to refer briefly to conditions other than Addison's disease which have been ascribed to suprarenal insufficiency. It has been shewn that both in chronic exhausting diseases and in some acute diseases the medulla is devoid of adrenalin (Mott and Halliburton), and it is reasonable to believe that the asthenia, muscular and cardiovascular, in these conditions is in part due to a deficiency in adrenalin. For the group of symptoms not uncommon in chronic pulmonary tuberculosis and consisting in pigmentation, debility, and suggesting but falling short of those seen in Addison's disease, Boinet has suggested the name Addisonism, and recommends adrenalin as the proper treatment. Other chronic conditions characterised by asthenia and low blood-pressure, such as cyclical albuminuria and some forms of neurasthenia, have been tentatively explained as due to adrenal inadequacy, but, though attractive, this interpretation has not been proved.

That acute suprarenal inadequacy occurs is highly probable; thus, in diphtheria the medulla of the suprarenals has been found to be devoid of adrenalin, and it has been shewn empirically that the most satisfactory treatment for cardiac failure in this disease is adrenalin. It also seems

probable that some of the symptoms in acute adrenal haemorrhage (*vide* p. 425) are due to sudden cutting off of the normal supply of adrenalin.

Hyperplasia of the suprarenals has in a few instances been associated with excessive growth of the sexual organs; this correlation is interesting in connexion with the occurrence of sexual precocity and overgrowth in some children with malignant hypernephromas of the suprarenal cortex (*vide* p. 432). Hyperplasia of the cortex is seen in cases of renal disease and it has been produced by experimental damage to the kidneys (Darré); it has therefore been thought that auto-intoxication of renal origin sets up hyperplasia of the cortex (*vide* also p. 427). From animal experiments Marrassini concludes that interference with renal excretion increases the functional activity of the medulla, and Schur and Wiesel find that the blood-serum of patients with chronic renal disease dilates the pupil just as adrenalin does; this suggests that the blood contains adrenalin. Hypertrophy of the medulla of the adrenals has been described in cases of high blood-pressure with arteriosclerosis, granular kidneys, and hypertrophy of the heart by Wiesel, who, however, believes that the cardiac change precedes that in the suprarenals and is therefore not due to it. On the other hand, since it has been shewn conclusively that experimental injection of adrenalin produces arterial disease, it might naturally be surmised that a primary hyperplasia of the suprarenal medulla with excessive secretion of adrenalin might give rise to arteriosclerosis and eventually to granular kidney. There is, however, no proof of this attractive hypothesis. In other words there is no evidence of a disease of the adrenal medulla comparable to exophthalmic goitre.

Fatty Change.—In the suprarenals of adults fatty change in the cells of the cortex is so common as to be a physiological condition. The fat occurs as large globules in the cells and may be present throughout the whole of the cortex, or be best marked in the zona fasciculata; in children there is little fat normally. Fatty change does not give rise to any symptoms.

Haemorrhage into the suprarenals may occur in the following circumstances: (i.) As the result of severe injuries, such as fracture of the spine or rupture of the liver and spleen, blood may be poured out around or into the suprarenals, the haemorrhage being almost always in the medulla. (ii.) As the result of injury during birth, haemorrhages frequently occur into the suprarenals. In 105 still-born children Dr. H. Spencer found extravasations into these organs in 25, nearly always into the medulla; in half the cases it was bilateral; in 3 cases the haemorrhage had ruptured the capsule. These haemorrhages occurred more often in difficult labours, and were more frequently met with in pelvic than in cephalic presentations. (iii.) In chronic venous engorgement due to chronic cardiac or pulmonary disease. (iv.) In toxic and infective conditions. Experimentally the injection of diphtheria toxin and of various micro-organisms may be followed by haemorrhage into the suprarenals.

It is, therefore, not surprising that adrenal haemorrhages are occasionally seen in diphtheria, erysipelas, enteric fever, pneumonia, small-pox, congenital syphilis, scurvy, and burns. But in other cases the cause of suprarenal haemorrhage, though probably toxic or infective, is obscure. This condition may appear in adults but has been chiefly observed and studied in infants. From the occurrence of the lesion in a number of unvaccinated children, in 7 out of 10 cases collected by Dr. Riviere, the suggestion has been put forward that the cases are examples of rapidly fatal haemorrhagic small-pox (Andrewes); but of this there is no convincing proof. It has also been thought that the haemorrhages may be the result of food-poisoning, of intestinal infection, or of an acute toxæmia of unknown origin (Dudgeon). Bacteriological examination has in some instances been negative, and in others has revealed the presence of staphylococci, streptococci, or pneumococci. The haemorrhages may be punctate, interstitial, or massive, and unilateral though usually bilateral. The extravasation may spread into the tissues around and, no doubt, by irritating the sympathetic plexuses may produce symptoms like those of haemorrhagic pancreatitis; the haemorrhage may leak into the peritoneal cavity. If the patient survive it is conceivable that subsequent fibrotic changes in the adrenals might induce Addison's disease (*vide p. 397*).

The *symptoms* accompanying these acute adrenal haemorrhages vary to some extent, but the most characteristic are the sudden onset of fever, pain in the upper part of the abdomen, vomiting, convulsions, and diarrhoea; later, tympanites and collapse, followed by death within forty-eight hours of the onset. In some of the cases purpura is associated with the adrenal haemorrhage, and it would appear probable that they are both the results of a toxic or infective cause; but it has been thought, partly because the purpura may yield only to adrenalin, that the damage done to the adrenals plays a causal part in the haemorrhages (Loeper, Dudgeon). In suspected cases treatment should be directed to counteracting the collapse by warmth, stimulation, and the administration of adrenalin.

(v.) Haemorrhage may take place into benign or malignant hypernephromas.

Lardaceous Disease.—When attacked by lardaceous disease the suprarenal capsules appear but slightly increased in size, and have a somewhat translucent appearance on section. With the iodine test the cortex becomes a dark brown, while the medulla remains of a grey or greyish-yellow. The contrast thus presented is the reverse of that seen in health. The suprarenal bodies are among the organs which undergo the lardaceous change with comparative frequency. In 21 cases of well-marked lardaceous disease the suprarenal capsules were affected in 9; in 4 of the cases it was so slight that microscopic examination was necessary to determine its presence. It is always best marked in the vessels running vertically through the cortex; and, though it may be present in the medulla, it is always less marked there than in the cortex.

Cloudy Swelling.—In febrile conditions softening and cloudy swelling

occur in the suprarenals as in other organs. The medulla appears sodden and blood-stained, and, microscopically, small extravasations may be found in the cortex. The softening disposes to a separation between the cortex and the medulla, and thus even slight manipulation may produce a cavity. This finds a permanent record in the name capsule as applied to the suprarenal gland. In pyaemia small vascular streaks in the cortex, or more rarely minute abscesses due to embolism, may occur. In very rare instances *suppuration* in the suprarenals has been associated with severe symptoms somewhat resembling those of suprarenal haemorrhage.

Tuberculosis.—In generalised tuberculosis miliary tubercles may be seen in the suprarenal bodies.

In chronic tuberculosis, whether primary or secondary, the process begins in the medulla. Care must be taken not to regard as discrete caseous tubercles the small fatty adenomas so often seen projecting from the cortex. In the early stages of chronic tuberculosis the inflammatory granulation-tissue has a firm speckled appearance. Caseation, softening, or calcareous infiltration may all follow as in other tuberculous formations; but it is improbable that caseous material ever disappears entirely. Tuberculosis is frequently found in the adrenals without any signs or symptoms having been present.

In 400 cases of tuberculous disease of various parts of the body abstracted from the post-mortem books of St. George's Hospital by Mr. M'Kerrow and myself, secondary tuberculous caseous foci were found in 44 without any signs of Addison's disease. Arranging the cases in decennial periods, it is seen that in 97 cases in which death occurred under ten years of age tubercle was found in the suprarenals in 9 or 9·2 per cent; in 42 cases occurring between the ages of ten and twenty years tubercle was found 7 times or 16·6 per cent; in 72 cases between twenty and thirty years 4 times or 5·5 per cent; in 76 cases between thirty and forty years 11 times or 14·5 per cent; in 65 cases between forty and fifty years 6 times or 9 per cent; in 34 cases between fifty and sixty years 5 times or 14·7 per cent; in 14 cases between sixty and seventy years twice.

Syphilis.—Single or more rarely multiple small gummas are occasionally seen in the suprarenal bodies, and there may be general fibrosis. The *Treponema pallidum* has been found in the suprarenals in both acquired and in hereditary syphilis. Miliary gummas may occur in hereditary syphilis, and a remarkable case of a calcified gumma in an infant aged fifty-seven days has been recorded (Vinogradow). In inherited syphilis the organs may shew small-celled infiltration, congestion frequently, and in rare instances haemorrhages. Potier has figured much blood-pigment in the medulla. Jacquet and Sézary record the case of a syphilitic man who had signs of Addison's disease which disappeared on antisyphilitic treatment; he died two months later from cerebral haemorrhage, and at autopsy the suprarenals, which were enlarged and sclerosed and shewed the *Treponema pallidum*, were the only organs with syphilitic changes. In

rare cases *actinomycosis* occurs in the suprarenals; the right may be affected in association with the liver and it may be difficult to decide in which organ the infection started, though the liver is the more probable site. In cases of pyaemic streptothrix infection the adrenals may shew abscesses.

Ophüls refers to 3 cases of extensive caseation in the suprarenals due to *occidioidal* infection.

TUMOURS.—Tumours derived from the cells of the suprarenal glands are now usually classed in a group by themselves under the non-committal title of *hypernephroma* (Birch-Hirschfeld). Woolley has suggested the title *mesothelioma*.

Non-malignant tumours of the suprarenals may be divided into (a) *hypernephromas* which are not uncommon, (b) cysts, and (c) other rare growths.

(a) *Benign Hypernephroma or Adenoma*.—Several kinds occur; the first two, especially the first, are common, the others are rare.

i. Multiple small yellowish nodular projections, situated on the surface and in the substance of the cortex of the organ; they often shew advanced fatty change. In other respects the cells composing them are like the cells of the cortex. These adenomas pass by gradual transitions into the areas of nodular hyperplasia which, like them, specially occur in the suprarenals in advanced life. They are sometimes mistaken for tubercles undergoing caseation; in this connexion it is well to remember that chronic tuberculosis begins in the medulla.

ii. Large adenomas usually unilateral may be bilateral. Virchow described them under the name of *struma lipomatosa suprarenalis*. The presence of these adenomas is not uncommon in cases of generalised arteriosclerosis with granular kidneys; it has been suggested that they are the result of an attempt on the part of the cortex to neutralise the poisons responsible for the high blood-pressure (Aubertin and Ambard). It is quite clear that, as the cortex does not contain any adrenalin, these adenomas can have no influence in raising the blood-pressure. They form distinctly localised tumours which may attain a very considerable size. They arise in the cortex, often indent and displace the medulla, but do not invade it, and in arrangement usually resemble the zona fasciculata. They are a magnified edition of the small multiple suprarenal adenomas, which may coexist with them in the same organ. The cells contain glycogen, lecithin, and often a large amount of fat, which partly accounts for their pale yellow colour. Occasionally the fatty change is so advanced that they appear softened or necrosed. When this is the case, extravasation may occur into the substance of the organ, and large tumours with a malignant aspect and prone to form haemorrhagic cysts result; probably some cases formerly recorded as angiosarcomas without any secondary growths were in reality of this nature. These large adenomas are the only ones of any clinical importance. Commonly the ordinary adenomas have no more supporting fibrous tissue than the rest of the organ; but in other cases the quantity of fibrous tissue is

much in excess, so that the term fibro-adenoma may be used. I have seen an example of this variety in which the cells did not shew any fatty change, and in which hyaline degeneration of the vessels was well marked.

iii. Pigmentary adenomas arising from the zona reticularis. The cells contain pigment granules, but never shew fatty change. They may be multiple. Letulle described three cases, all in phthisical subjects.

iv. Adenomatous tumours of the medulla containing numerous vessels and epithelial cells. The veins may contain the hyaline material found in the veins of the medulla by Manasse. These tumours are rare, and, as some of them have probably been described as sarcoma or glioma, some doubt exists as to their classification.

Non-Malignant Tumours arising in Accessory Suprarenal Bodies, or in Suprarenal "Rests."—Accessory suprarenal bodies are found when looked for; but otherwise, as they are so small, they do not, as a rule, attract attention; according to Schmorl they are present in 92 per cent of all bodies. They are yellow in colour, oval or round, and usually about the size of a grain of corn. I have seen one as large as a cherry, but this is very exceptional. The larger ones contain a medulla.

The accessory suprarenal bodies may be found in the immediate neighbourhood of the two organs, among the fibres of the renal or solar plexus, in close relation to the semilunar ganglia, and in contact with the inferior vena cava. They have been found in the mesentery, the broad ligament of the uterus, on the ovarian or spermatic vessels near the inguinal canal, and even on the epididymis.

Benign cortical hypernephromas have been found in the broad ligament (Marchand), and in the inguinal canal (Lockwood). Eurich has described a tumour arising in the medulla of an accessory suprarenal body.

Instead of being in the loose connective tissue, accessory suprarenal bodies may be found embedded in the kidney, liver, or head of the pancreas, and are then often spoken of as suprarenal "rests." Suprarenal remnants are comparatively common in the kidneys, if carefully looked for. They may be composed of cortex only, or of both cortex and medulla. Occasionally an extension of the main adrenal is found under the capsule of the kidney. They must, however, be distinguished from inspissated cysts in the renal cortex. In the liver they are less often seen; Schmorl found them in 4 out of 510, and Beer in 6 out of 150 autopsies.

In the kidney they may grow and give rise to innocent tumours; some so-called renal adenomas and lipomas are thus explained, and have been called Grawitz's tumours. In the case of the so-called lipoma the cells of the suprarenal "rest" undergo extensive fatty change. But true lipomas of the kidney do occur, and a true lipoma and a hypernephroma may as the result of a simultaneous inclusion be present in the same kidney; it has also been suggested that the cells of a renal hypernephroma may undergo metamorphosis into true fat-cells (Keenan and Archibald). Five cases of cystic hypernephromas of the kidney imitating

various cystic conditions of the organ have been collected by Weil. These benign hypernephromas may remain latent for a long period and then become malignant and grow rapidly. Reference will be made later to malignant tumours arising in suprarenal "rests." Benign hypernephromas in the liver have been described (Schmorl, de Vecchi).

(b) *Cysts* are rare; the following forms may be mentioned:—(1) Parasitic; hydatid cysts primary in the adrenals have been recorded but are pathological curiosities. (2) Embryonic cysts due to inclusion of cells of the Wolffian body; a small cyst lined with ciliated epithelium has been described (Sick). (3) Cystic lymphangiomas; Terrier and Lecène have collected 4 cases. The cysts may reach a large size, may be uni- or multi-locular, and shew smooth muscle in their capsule. The contents are serous, but may become haemorrhagic. (4) Pseudo-cysts due to softening of an adenoma; these cysts may be small and contain serous or turbid fluid. Dr. Bosanquet has collected the few recorded cases. From haemorrhage into these cysts large tumours may form, but it may be difficult to decide whether an adenoma existed prior to the haemorrhage. Hypernephromas, both malignant and non-malignant, are very liable to necrosis, autolysis, haemorrhage, and pseudo-cyst formation. (5) Cysts may result from haemorrhage into a healthy adrenal, and, according to Terrier and Lecène, may contain many pints of fluid. The cyst walls may become calcified. These cysts are always unilateral.

(c) Other tumours of the suprarenals, such as glioma, fibroma, fibromyoma, ganglionated neuroma, and angioma, have been recorded, but are pathological curiosities. Angiomas in both adrenals have been found in association with similar tumours in the liver (Payne, Petroff). In Petroff's case Addison's disease was diagnosed.

Primary Malignant Tumours.—The nomenclature of these tumours has given rise to considerable discussion, and difficulty has been experienced in classifying them under the usual heads of carcinoma and sarcoma. Primary malignant tumours probably arise more often in the cortex which is mesoblastic than in the medulla which is neuro-ectodermal; tumours of the cortex would naturally be classed as sarcomas, endotheliomas, or peritheliomas, but histologically these tumours may resemble carcinoma, or the same tumour may shew the structure of carcinoma in one part and of sarcoma in another. If any of the names in general use for malignant tumours be employed, perithelioma is the most suitable. The primary malignant growths of the medulla are histologically more allied to gliosarcoma than to carcinoma. It is obvious that these tumours form a special group, and it is probably most convenient to describe them simply as malignant hypernephromas.

Age and Sex.—No period of life is exempt. The oldest case of which I have a note was in a man aged 75 years (Scudder). Cases in young children constitute a definite group and, as will be seen later, may present peculiar clinical features. There is probably also a distinct group of cases of congenital malignant disease of the suprarenals and liver; the characteristic of these cases is that it is uncertain in which of the two organs the

growth commences. Pepper has collected 6 such cases and contrasts them with 46 other cases of primary sarcoma of the adrenals. In 32 cases in adults collected by me the average was 47·2 years. In Ramsay's 62 collected cases 36 were males and 26 were females. In 23 cases of primary malignant disease of the suprarenals in early life, collected by Drs. Bulloch and Sequeira, females (17) were nearly three times more numerous than males (6). In adult life the incidence seems to be more marked in the male sex ; in 32 cases which I have tabulated 19 were in men and 13 in women.

Morbid Anatomy.—Malignant hypernephromas may arise either in the cortex or in the medulla, but are commoner in the cortex. It appears that they may be derived from innocent hypernephromas, and may therefore be encapsuled in parts whilst shewing evidence of malignancy in others by infiltrating the liver or adjacent organs. The appearance of these growths is characteristic ; originally the prevailing colour is a dull whitish-yellow, but there may be varying amounts of haemorrhage into the growth which may become little more than a blood cyst. Necrosis, autolysis, and the formation of pseudo-cysts are specially prone to occur. The tumour may reach a very considerable size ; it has been known to weigh 9 lbs. (Dreschfeld and Moore). The growth may extend into the suprarenal vein and so, on the left side through the renal vein, into the inferior vena cava ; metastases in the lungs are thus readily set up. Prof. Adami has given me the details of a case of primary malignant disease of an accessory adrenal in which the growth extended into the inferior vena cava and gave rise to retrograde embolic growths in the branches of the hepatic veins. On the right side the growth not uncommonly extends by continuity into the right lobe of the liver. Invasion of the upper end of the adjacent kidney is rare, and as the fibrous capsule of the kidney resists invasion the kidney may be flattened and displaced without being infiltrated. Doubt may arise whether a hypernephroma invading the liver and the upper pole of the right kidney started in the suprarenal or in a suprarenal rest in the kidney. But in some cases a suprarenal tumour does invade the kidney ; this occurred in 4 out of 26 cases collected by Dr. Marks and myself. On the left side a malignant hypernephroma does not appear to invade the spleen. In rare instances the growth spreads into the pancreas and most exceptionally into the stomach. In 32 cases tabulated by me the growth was on the right side in 16, on the left side in 13, and in both suprarens in 3.

Metastases may be widespread ; secondary growths occur in the liver, lungs, pleurae, lymphatic glands, kidneys, skin, and exceptionally in the central nervous system and heart. Special interest attaches to secondary metastases in bones, as this is comparable to the well-recognised association of carcinoma of the thyroid and skeletal metastases. Scudder has collected a number of cases, and Dr. Hutchison has tabulated 10 cases of children with secondary growths in the skull and proptosis. The bony metastatic growth may be the first thing wrong that is noticed, and may be the only form of metastasis.

Conditions of the other Suprarenal.—As already mentioned, simultaneous affection of both suprarenals by a primary growth has been described in a few cases. Possibly in some instances it may be difficult to distinguish between secondary invasion of the other adrenal and bilateral primary growths. Occasionally the other adrenal shews a manifestly secondary growth. In a few cases the other adrenal, though free from growth, is enlarged as if compensatory hypertrophy had taken place.

The histological structure of malignant hypernephromas shews considerable diversity ; this depends in the first instance on the composite nature of the suprarenal gland. Tumours may start in the cortex or in the medulla. Malignant hypernephromas of the cortex may in parts shew the structure of an adenoma of the cortex ; the cells contain glycogen and their clear protoplasm stamps them as unmistakably adrenal in origin. In other parts active growth is seen, and the arrangement and form of the cells become atypical to correspond with the malignant character of the growth. There may be giant cells and spindle-shaped cells, and haemorrhage, necrosis, and autolysis may so greatly modify the appearances of the growth, that the characteristic adrenal nature of the cells may be lost. The malignant hypernephromas of the cortex are generally somewhat alveolar in arrangement and have in the past usually been described as carcinomas or more recently as peritheliomas. Malignant hypernephromas of the medulla are less distinctive from a histological point of view as they do not present such easily recognisable cells as those in cortical hypernephromas. Malignant tumours of the medulla have usually been described as sarcomas. Hypernephromas contain fat, lecithin, cholesterol, and glycogen.

Clinical Picture.—There is a tumour in the kidney region. In rare cases a lump has been present for a very considerable time, even for years, before it takes on rapid growth or leads to metastases. In a few instances a secondary growth is the first sign or symptom to be noticed, and when it is in the orbits may, as in one of Dr. Hutchison's cases, lead to examination of the abdomen and the detection of the primary tumour. The tumour is very difficult to differentiate from a renal tumour, which is of course commoner, and in most cases this cannot be done. It was at one time suggested that an adrenal tumour would depress the colon downwards instead of displacing it forwards as a renal tumour does, but this is certainly not sufficiently constant to be of any value.

Much discussion has been devoted to the question whether Addison's disease is closely imitated by primary new growths of the suprarenals. The complete clinical picture is not presented, but some of the symptoms of Addison's disease may be present. Thus, in his study of 67 cases Ramsay found that marked and steady loss of strength and debility were the most constant symptoms. Vomiting is occasionally present, and pain in the back is not rare. Pigmentation of the skin is quite exceptional in adults, but it was present in a man aged fifty-seven years (L. Dickinson). It has been suggested that the reason why malignant hypernephromas do

not give rise to Addison's disease is that the tumour cells continue the functional activities of the adrenals, just as thyroid tumours continue to form thyroiodin ; but this compensatory action, as far as regards the formation of adrenalin, would only hold good as regards hypernephromas arising in the medulla, which are less often seen than those with the structure of the cortex. Although it is an obvious suggestion that high blood-pressure might be produced by hypernephromas of the medulla, this has not been satisfactorily established.

In children there is a well-defined group of cases characterised by precocious growth of the body generally, and of the sexual organs in particular, with overgrowth of hair and fat and pigmentation of the skin. Drs. Bulloch and Sequeira have collected 10 such cases, all but 2 under eight years of age, and 8 of them girls. The extreme sexual development is probably connected with the origin of the malignant hypernephroma in the cortex, the cells of which are closely related to the sexual glands. These cases of precocious bodily growth have been further divided into (1) the obese form, met with in both sexes, but apart from the presence of pubic hair the precocious sexual development is not marked ; and (2) the muscular or infant Hercules form occurring in males, and always shewing true sexual precocity (Weber; Guthrie and Emery). It is, however, quite exceptional to get any analogous changes in adults with hypernephromas ; K. Thornton recorded the case of a woman aged thirty-six years who was covered all over with black silky hair and had to shave her face, and Dr. Richards refers to a similar condition in a female lunatic aged thirty-two years. As already mentioned, Dr. Hutchison has isolated a further group of cases in children characterised by secondary growths in the skull and proptosis. These cases may resemble (a) chloroma, from which a blood count will distinguish them by shewing an absence of lymphocytosis, and (b) infantile scurvy, which can be excluded by the absence of other signs and the failure of antiscorbutic remedies.

In malignant hypernephromas the temperature may be irregular or considerably raised for a time, probably when rapid growth or necrotic and autolytic changes are going on in the tumour. The tumours may form large cysts and may push the diaphragm up and so embarrass respiration. In the later stages there may be considerable wasting and oedema of the feet.

As a general rule it may be stated that these tumours do not cause haematuria, though hypernephromas embedded in the kidney may invade the renal pelvis and give rise to blood in the urine. But independent changes in the kidney were responsible for haematuria in 2 of the 67 cases collected by Ramsay, and albuminuria and haematuria have been recorded from invasion of the kidney by a hypernephroma (Dreschfeld and Moore).

These cases run a rapid course and prove fatal by exhaustion and secondary growths within six months from the time of onset of symptoms, often sooner. The exception to this rule is in the rare cases in which a

presumably non-malignant hypernephroma has been palpable as a tumour for some time before active malignancy sets in.

As already mentioned, the *diagnosis* of these tumours from renal growths is very difficult. In the interesting group in which anomalies of growth and sexual development are associated with a hypernephroma, the nature of the abdominal tumour is made highly probable by the accompanying signs. Diagnosis from hydatid cysts, pancreatic cysts, and enlargement of the gall-bladder may give rise to considerable difficulty in certain cases. When a malignant hypernephroma on the right side has extended into the liver it may imitate a growth or other cause of enlargement of the liver.

The *prognosis* of malignant hypernephromas is very bad, and is worse than in primary malignant disease of the kidney (Morris). Removal is the only means to be adopted, and the operation is rather a severe one; on the right side the suprarenal normally passes under the inferior vena cava, and hence the operative removal of a right hypernephroma is dangerous if complete, and is likely to be followed by local recurrence when part of the organ is left. Metastasis often occurs early, and in some of the cases that have survived operation secondary growths were present at the time of the operation, and in others recurrence has been very rapid. Of 23 cases of removal of various suprarenal tumours 12 were fatal from operation and 5 shewed rapid recurrence (Wendel).

Malignant Tumours of other Organs arising in Suprarenal "Rests."—Besides giving rise to "lipoma" or adenoma of the kidney, displaced accessory suprarenals or "rests" may be the origin of malignant growths in the kidney, which may be spoken of as renal hypernephromas. Their structure resembles that of primary malignant disease of the suprarenal bodies, and they shew the same tendency to the formation of haemorrhagic cysts and to undergo necrosis. The same difficulty arises here, as in the case of malignant disease of the suprarenals, in definitely assigning the tumour either to the group of the sarcomatous or to that of carcinomatous growths. What has been said about the morbid anatomy of malignant hypernephromas applies in almost every particular to malignant hypernephromas in the kidney. It is perhaps less rare for a renal hypernephroma to persist for some time as an innocent tumour and then grow rapidly; renal hypernephromas are seldom seen in childhood, and are not accompanied by the remarkable hirsuties and anomalies of physical growth mentioned above in connexion with hypernephromas of the cortex of the suprarenal body. (For clinical features, see p. 711.)

As prophesied by Schmorl, cases of primary malignant disease of the liver have now been shewn to arise in accessory adrenal tissue embedded in the liver. Pepere described the first case, and since then others have been put on record (Phillips and Spilsbury, White and Mair). Probably a certain number of retroperitoneal growths have started in accessory adrenals. Malignant hypernephromas arising primarily in the pelvis have been described (Chiari, Eastwood).

Secondary growths in the suprarenal bodies are not uncommon. In 100

cases of carcinoma of various parts of the body secondary growths in the suprarenal bodies occurred ten times, and in 35 cases of sarcoma five times. Dr. Norman Moore, in 102 cases of carcinoma, found secondary growths in 3; and in 21 cases of sarcoma five times—3 sarcoma, 2 endothelioma. It appears probable, therefore, that secondary growths are commoner in sarcoma; this is easily explained by the extensive blood-supply of the suprarenal bodies taken in conjunction with the spread of sarcoma by the blood-vessels. The relation of Addison's disease to secondary growths in the suprarenal bodies is dealt with on page 400.

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H. D. R.

DISEASES OF THE SPLEEN

By H. D. ROLLESTON, M.D., F.R.C.P.

I. THE GENERAL PATHOLOGY OF THE SPLEEN.—*General Remarks. Effects of splenectomy in man. The condition of the spleen in bacterial infection and in toxæmia. The part of the spleen in bacterial infection and in immunity. The part of the spleen in the various forms of anaemia. Relation of the spleen to the liver and alimentary canal.*

General Remarks.—From a consideration of their structure and functions the ductless glands may be divided into two categories—(i.) those of an epithelial type which have an internal secretion, such as the thyroid, suprarenal, and pituitary glands; and (ii.) those containing lymphoid tissue which are not known to possess any special internal secretion—the spleen and the thymus gland.

There appears also to be a general difference in their pathological relations; the spleen and thymus are affected and undergo alteration rather as the result of disease elsewhere than as its cause; whilst in the case of the thyroid, suprarenal bodies, etc., we have chiefly to deal with primary morbid conditions and diseases, such as myxoedema or Addison's disease, initiated in these organs, which lead to general and secondary changes elsewhere. It would be unwise, in the present state of our knowledge, to press this distinction too far, and to assert too dogmatically that there is not such a thing as primary disease of the spleen; for until our knowledge of the physiology of the spleen is in a more satisfactory state the problems of its pathology must necessarily present great difficulties. But we may safely consider the spleen as an organ prone to respond to disease of other parts, especially of the blood and the haematopoietic organs of the body, and but little liable to independent primary affections.

Effects of Splenectomy.—That the spleen is not essential to life, and that its removal does not affect development, has been shewn experimentally in animals, and as the result of splenectomy in human beings whether for disease of the organ or for traumatic rupture. The effects of experimental splenectomy have been extensively investigated. The results are not uniform, for whilst many of the older observers described some degree of anaemia and leucocytosis, more recent workers (Noel Paton, Gulland and Fowler, and Biagi) conclude that removal of the spleen has no influence on the numbers of red blood-corpuscles and leucocytes. Kurloff found that in guinea-pigs the spleen has little to do with the formation of leucocytes, and that after splenectomy compensation occurs only in the lymphatic glands, followed in the second year by a marked eosinophilia.

After experimental removal of the spleen numerous small red masses

have occasionally been found in the omentum; they were originally regarded as newly formed splenunculi, but they are probably new haemolymph glands (Warthin). The results of splenectomy in man can hardly be regarded as exactly comparable with those of experimental removal of the organ in normal animals. In man the operation is either performed for rupture of a previously healthy viscus, in which case there has usually been very considerable haemorrhage which of itself necessarily leads to temporary blood changes; or for disease, in which case either the organ has undergone more or less morbid change, so that compensation for its lost function may have already taken place, or there may be morbid changes elsewhere in the body which interfere with the blood-picture.

From an analysis of a large number of cases of splenectomy for rupture it appears that as a rule the patients only shew a transient anaemia and leucocytosis which passes off in about a month, and enlargement of the lymphatic glands. This condition, however, is not constant. In some cases eosinophilia appears, usually after some months. In 5 instances out of 70 cases collected by Mr. Simpson, additional and remarkable manifestations supervened on or after the tenth day, comprising progressive loss of weight, anaemia, fever, rapid pulse and respiration, thirst, headache, drowsiness, griping pains in the abdomen, and tenderness over the long bones thought to indicate hyperplasia of the red marrow. In some instances there is swelling of the thyroid. These unusual sequels certainly suggest that some form of infection had taken place. Examination of the urine in a case of splenectomy for rupture did not shew any striking variation from the normal (Mendel and Gibson), thus agreeing with the results of Prof. Noel Paton's experimental investigation.

The Condition of the Spleen in Bacterial Infection.—In acute fevers and in bacterial infection there is a general tendency to an accumulation of micro-organisms in the spleen; this, for example, is especially well marked in septicaemia, infective endocarditis, enteric fever, malaria, and trypanosomiasis. The micro-organisms found in the organ are by no means limited to the one giving rise to the specific disease; thus, in enteric fever streptococci and staphylococci may be present. Some of the microbes are free, others are enclosed in cells. It does not follow, however, because micro-organisms are found in the spleen that they are constantly present in the blood.

This microbic occupation is accompanied by well-marked hyperaemia and swelling of the organ, even to such an extent that in rare cases rupture has occurred spontaneously. In children the capsule of the spleen is more extensible than in older people, and the enlargement therefore is relatively better marked. This condition is sometimes spoken of as acute splenic tumour. On section the spleen is soft and the pulp is sometimes so diffused as to run away. In some experiments on pneumococcal infection in rabbits Washbourn found that the spleen might be either softened, as here described, or firm and normal in

consistency. This latter condition may somewhat exceptionally be met with in man; in cholera the spleen is firm and somewhat diminished in size, probably from the concentration of the blood, and in dysentery, and yellow fever, the organ is not enlarged.

In bacterial infection the colour of the spleen on section is either that of marked congestion, or greyish from increase of leucocytes in its substance. The Malpighian bodies are prominent and swollen in some cases, whilst in others they can only be seen with difficulty. In addition to the accumulation of micro-organisms in the spleen, changes in its histological structure occur; these are due to the effects of the toxic products of bacterial activity. That they are independent of the presence of bacteria in the organ, is shewn by their occurrence after the injection into the circulation of toxins only.

The pulp becomes engorged with blood-corpuscles and phagocytes, partly leucocytes and partly derived from endothelial proliferation; there is active phagocytosis of red corpuscles, neutrophil leucocytes, and bacteria. There is mitosis and proliferation of the endothelial cells of the pulp and of the lymphoid cells of the Malpighian bodies leading to a zone of basophil cells larger than the ordinary lymphoid cells of the follicle (Muir); Dominici regards these cells as potential myelocytes which wander into the pulp and form polymorphonuclear neutrophils, but Prof. Muir does not find sufficient evidence of this. There is no doubt that nucleated red blood-corpuscles and myelocytes are present in the spleen in infections, but divergent opinions have been expressed as to their significance. Prof. Muir concludes that they have merely been washed out of the bone-marrow and caught in the spleen; whilst Dominici considers this "myeloid transformation" of the spleen to be a return of the cells of the organ to the haematopoietic function possessed in fetal life, the myelocytes and nucleated red cells being produced in the spleen and forming leucocytes and erythrocytes. In malaria there is a large quantity of discharged blood-pigment.

Condition of the Spleen in Toxaemia.—Since the hyperaemia and consecutive changes in the spleen in bacterial infection are due to the products of bacterial activity, it would be natural to expect that in sapraemia and in toxæmia a somewhat similar change would occur in the spleen. That the organ is invariably enlarged in toxæmia, apart from the presence of bacteria in the spleen, is contrary to experience; but in some conditions, probably or possibly of this nature—such as Hanot's hypertrophic biliary cirrhosis, polycythaemia with cyanosis (*vide art. Vol. V.*), and very occasionally in exophthalmic goitre—the organ is enlarged.

Flexner, in an experimental study of the tissue-changes produced by the injection into the circulation of ricin and abrin, phytalbumoses obtained from the seeds of the castor-oil plant and the jequirity bean (*Abrus precatorius*), found the spleen uniformly swollen and soft, the swelling apparently being of the splenic pulp. Whilst bacterial toxins, such as diphtheria toxin, affect the Malpighian bodies more than

the pulp, the reverse is the case in intoxication with ricin, abrin cantharidin, and corrosive sublimate (Lyon), in chronic poisoning with which the splenic pulp is crowded with granules and globules of yellow pigment inside the cells. This pigment gives a blue colour with ferrocyanide of potassium and hydrochloric acid, which may be regarded as the evidence of great haemolysis. As a result of poisoning dogs with metatoluylenediamine, paraphenylenediamine, and nitrite of sodium, Pilliet found that the Malpighian bodies become atrophied, and thus that a kind of fibrotic atrophy results. In experimental anaemia due to toxic bodies the spleen appears to revert to its fetal function of forming red blood-corpuscles. In rabbits with anaemia due to repeated doses of saponin given intravenously the sinuses of the spleen were much dilated and crowded with marrow cells, chiefly erythropoietic, but megalokaryocytes and leucocytes were also present; there was evidently vicarious blood-formation going on in the spleen (Bunting). Similar results were obtained by Morris in experimental anaemia due to the haemolytic agent pyrodin. On the other hand, in uraemia, the most familiar example of a purely chemical toxæmia, no splenic enlargement occurs.

In considering these discordant data, it must be borne in mind (a) that the effects of various poisons are likely to be different, and (b) that in toxæmia the poison reaches the spleen in a very dilute form when compared with its relative concentration when the spleen is occupied by active micro-organisms. We can only conclude that in toxæmia the spleen may be affected as in bacterial infection, though by no means constantly.

As a result of long-continued bacterial infection, or toxæmia, the spleen may shew a varying degree of fibrosis.

The Part of the Spleen in Bacterial Infection.—The spleen is, generally speaking, so altered in fevers and in cases of bacterial infection, that the question naturally arises whether this is merely a secondary change, or whether special and defensive processes take place in the spleen. Does the spleen play any special part in the defence of the organism which is distinct from that played by lymphatic tissue elsewhere?

In cases of general haemic infection the spleen and liver are perhaps the organs most extensively occupied by the micro-organisms. This is well seen in anthrax and in streptococcal septicaemia. Is this merely a stagnation of the microbes in the lax, open tissue of the spleen? Or is there in addition a multiplication of the microbes and a manufacture of toxins and bacterial products in the spleen, so that removal of the organ might diminish the toxic process? The observation that in malaria splenectomy is followed by a diminished toxicity of the urine (Jonnesco) lends some support to this hypothesis. Or, on the other hand, is an extensive destruction of micro-organisms taking place in the organ? Or are both these processes going on? If so, is the spleen, so to speak, the battlefield where the struggle between the invading micro-organisms and the defensive powers of the body is fought out? That the spleen

is a kind of resting-place into which micro-organisms, which have gained an entrance into the blood, may get swept and left is shewn by injecting harmless microbes into the circulation of an animal. They rapidly disappear from the circulation, but may be found weeks after stowed away in the spleen, liver, and marrow of bone. As has been already seen, extensive phagocytosis goes on in the spleen, so that the organ plays a part in the defence of the organism against infection. Dr. Hankin and others have obtained a bactericidal substance from the spleen which is the same as the tissue fibrinogen of Wooldridge, or Halliburton's nucleo-albumin obtained from lymphatic glands, liver, kidney, and so on. The further question to be answered is, whether the spleen has any protective or defensive power other than that possessed by the lymphoid or other tissues generally.

In order to determine whether the spleen plays a special part in *natural immunity*—in the defence of the organism against infection—numerous experiments on animals have been performed. Bardach came to the conclusion that removal of the spleen renders the animal less resistant to infection; an effect attributed to a diminution of the area of phagocytosis. This writer considered that the part of the spleen in infections is phagocytic, that micro-organisms are taken up there by macrophages and microphages just as they may be seen to be in the spleen of malaria and relapsing fever, and that they are thus destroyed. Bardach was opposed to the view that in bacterial infection any chemical bactericidal body is manufactured by the spleen.

On the other hand, to take a few of many examples, Tiotine injected the blood of relapsing fever containing the *Spirochaeta obermeieri* into the circulation of monkeys whose spleens had been removed, and found, contrary to the results of Soudakewitch and Metchnikoff, that they recovered—though, it is true, not so readily as ordinary monkeys—and that subsequently they became immune. Montuori found that the bactericidal power of the blood of dogs and rabbits remained normal for fifteen days after splenectomy, as shewn by its action on typhoid bacilli and the cholera vibrio; that it then diminished and disappeared. This, however, was but a passing phase, and in four months from the splenectomy it had regained its normal power. These changes were more rapid in young than in old animals. Experiments on rabbits that had been splenectomised, and were, after varying intervals, inoculated with different micro-organisms, led to discordant results. Thus, twenty-five days after splenectomy, a rabbit was less resistant than normal to *Bacillus pyocyaneus*, while it had regained its usual resistance to *Staphylococcus pyogenes* (Courmont and Duffau). In a series of dogs and rabbits in which splenectomy was followed by experimental infection with Fraenkel's pneumococcus and the *Bacillus typhosus*, the results were practically the same as in animals similarly infected but whose spleens had not been removed; any slight differences that did occur appeared to depend on variations in the interval between splenectomy and the subsequent infection (Gueorgaievsky). The question whether the spleen

plays any protective part against trypanosome infection has given rise to divergent opinions. Rodet and Vallet state that, even apart from phagocytosis, the spleen exerts an extracellular trypanolytic action, whilst Laveran and Thiroux come to diametrically opposite conclusions, namely, that the course of trypanosomiasis is in no way different in splenectomised and in normal animals, and that splenic extract has no trypanolytic effect.

Tizzoni and Cattani considered that their earlier experiments shewed that the spleen played an important part in *acquired immunity*. They were unable to render rabbits, whose spleens they had previously removed, immune against tetanus. It thus appeared possible that the spleen might have the power of manufacturing some substance necessary to render the organism immune. Tizzoni and Cattani subsequently modified their previous opinion considerably, and came to the conclusion, which Righi also shared, that removal of the spleen merely acts like any other severe lesion, and reduces the general resisting powers of the organism temporarily ; but that it does not produce any permanent or specific change in the protective powers of the animal. (*Vide* also Vol. II. Part I. p. 16.)

Kanthack, working with rabbits and the *Bacillus pyocyaneus*, found that splenectomy, whether before or after protective inoculation, has no effect on the resulting immunity, and does not interfere in any way with the process, the temperature curve and leucocytosis being unaffected. Biagi found that in dogs splenectomy did not interfere with the production of haemolytic, bacteriolytic, or agglutinative bodies.

From a consideration of all these data, it appears highly probable that the spleen has no special protective power, either in natural or acquired immunity, which cannot be vicariously assumed by other organs, such as the lymphatic and haemolymph glands. The spleen, in fact, is and behaves like a lymphatic gland broken up and embedded in erectile tissue. The Malpighian bodies and adenoid tissue play much the same part that lymphatic glands do elsewhere ; and the open, loose, vascular tissue of the organ serves rather as a filter in which various bodies are deposited by the blood, perhaps to remain, perhaps to undergo subsequent changes.

The Part of the Spleen in the various Forms of Anaemia.—Since the spleen is so closely associated with the blood, and shares in its changes, it is only natural to inquire whether any causal relationship may exist between changes in the spleen and anaemia. If the normal function of the organ be in some way connected with destruction of blood-corpuscles, might not an exaggeration of this function give rise to anaemia ?

In traumatic anaemia the spleen, of course, cannot be supposed to play any causal part. With regard to the possibility of its playing any compensatory part in the formation of red blood-corpuscles, as stated years ago by Bizzozero, considerable scepticism has been expressed ; Dominici and others have investigated the subject again from an experimental standpoint, and find evidence that the splenic pulp shews

"myeloid transformation" or contains the haematopoietic cells present in red marrow, and reverts to its fetal function of blood formation.

Anaemias associated with splenic enlargement form a group of morbid conditions which have these two prominent features in common. Very various underlying conditions may give rise to what was formerly spoken of as splenic anaemia ; this is particularly the case in children, in whom anaemia and splenomegaly may be due to syphilis, or be associated with rickets and intestinal disorders. The forms of anaemia associated with splenic enlargement will be fully discussed in a special article in Vol. V., so that it is unnecessary to consider the subject here. In some cases there is splenomegaly and anaemia of some duration without any obvious cause, and the question then arises whether some form of infection has taken up its headquarters in the spleen and produced both the local lesions there and the blood changes. This applies to the condition spoken of as chronic splenic anaemia of adults, the existence of which, as a distinct disease, has not been unassailed ; some authors, indeed, have asserted that it is always part of some latent form of hepatic cirrhosis. No doubt cases conforming to the requirements set down for splenic anaemia have been proved to be the manifestations of syphilis, but there is equally no question that in others no cause is forthcoming on autopsy. It is in such instances that it seems justifiable to imagine tentatively that some as yet unrecognised parasite, possibly from the alimentary canal, has reached the spleen, and there remained to multiply and cause splenomegaly and anaemia. If this really occurs, the spleen, by being the main focus of disease, would play a primary part in the anaemia. Cases in which splenectomy is followed by disappearance of anaemia and diminution in the toxicity of the urine (Perez) certainly favour this hypothesis. But in the present state of our knowledge it would be unwise to go farther than this, for in the absence of any evidence of infection of the spleen in these cases, it cannot be denied that the condition might be one of chronic intoxication of intestinal origin, and thus comparable to polycythaemia with enlarged spleen.

In chlorosis all the evidence is to shew that the formation of red blood-corpuscles, and especially of haemoglobin, is at fault, and there are no grounds for thinking that increased haemolysis plays any part.

In pernicious anaemia it is perhaps less unlikely that the spleen may play a part in the production of the disease, but there is as yet no absolute proof that it does so. If Dr. W. Hunter's view be adopted that pernicious anaemia is essentially haemolytic in nature, and due to destruction of the red blood-corpuscles in the portal system by means of a poison absorbed from the alimentary canal, we may ask whether the spleen plays any part in the process. In normal conditions the spleen appears to remove dying red and white blood-corpuscles from the circulation, and to dispose of the haemoglobin, but there is no satisfactory evidence of an active haemolytic process in the organ. When there is an exaggerated haemolysis going on in the portal system, does the spleen

play any special part? In pernicious anaemia the spleen contains an increased amount of altered blood-pigment (haemosiderin). But there is no proof that an active haemolysis takes place there. A large number of red blood-corpuscles damaged by contact with haemolytic toxins reach the spleen, and therefore increased phagocytosis of these corpuscles goes on in the spleen. This process may lead to what is called a spodogenous enlargement of the organ. In this respect the spleen behaves like the haemolymph glands, only it is a much larger organ. Microscopically, the spleen may shew the presence of cells—nucleated red blood-corpuscles, myelocytes, megalokaryocytes—derived from the red marrow of bone (Meyer and Heineke), but they are compensatory and due to the anaemia, not in any way accountable for it. It cannot be said that there is any positive evidence to prove that in pernicious anaemia there is excessive haemolysis limited to the spleen.

In conclusion, there is no evidence that the spleen plays any part at all in the production of chlorosis or of traumatic anaemias; but it appears possible that in the various forms of anaemia associated with splenomegaly the spleen may be the main focus of infection or intoxication. There is no reason to believe that pernicious anaemia is due to changes primary in the spleen.

The relation of the spleen to the liver may be briefly referred to under two heads: (a) Morbid conditions of the spleen may be secondary to changes in the liver; in portal cirrhosis the spleen is generally enlarged (*vide p. 449*), and shews proliferation of the reticular tissue with fibrosis. As pointed out elsewhere, the splenic changes are probably due to venous engorgement in part only, and are also toxæmic; the poison responsible for the inflammatory changes in the organ may reach it by the splenic artery. In guinea-pigs ligature of the common bile-duct has been found to give rise to splenomegaly with the microscopic changes seen in infections (Ribadeau-Dumas and Lecène). It has even been suggested that in some cases of splenomegalic jaundice the splenic enlargement is compensatory in order to antagonise the haemolytic action of the bile acids, and that in jaundice the spleen increases the resistance of the red blood-corpuscles and confers antihaemolytic properties on the blood serum. (b) Hepatic changes may be due to disease of the spleen. Chauffard suggested that in some cases hepatic cirrhosis is secondary to poisons conveyed to the liver from the spleen, and instanced the hepatic changes in malaria, and Banti's disease or the terminal hepatic cirrhosis in cases of chronic splenic anaemia; further, in conjunction with Castaigne, he shewed that tubercle bacilli introduced into the spleen may set up hepatic tuberculosis, thus imitating the secondary infection of the liver seen in some cases of primary massive tuberculosis of the spleen in man (*vide p. 454*). Another illustration of the spread of a morbid process from the spleen to the liver is seen in the "Gaucher" form of chronic splenic anaemia, in which the extreme endothelial proliferation in the splenic sinuses may be accompanied by proliferating endothelial

cells in the portal vein and endothelial proliferation in the lymphatics of the portal spaces in the liver. There is a form of hypertrophic biliary cirrhosis, spoken of as metasplenomegalic, in which the splenic enlargement precedes any manifest change in the liver; the condition is allied to splenomegalic jaundice in which there is jaundice of prolonged course, sometimes congenital and hereditary, and splenomegaly. Lortat-Jacob and Sabareanu reported congenital jaundice in father and son; in the father the liver and spleen were both enlarged, in the son the spleen only. The earlier enlargement of the spleen in such cases suggests that a haemic infection of that organ is first set up, and that poisons produced there are conveyed to the liver, and set up cholangitis; it must, however, be admitted that the haemic infection may be responsible for the derangement in both organs, but that the effects are more marked in the spleen, and only supervene later in the liver.

Relation of the Spleen to the Alimentary Canal.—In great enlargement of the spleen mechanical obstruction to the outflow of blood from the cardiac end of the stomach may result from kinking of the *vasa brevia*; the intense engorgement of the cardiac end of the stomach thus set up has been given as an explanation of the recurrent haematemeses of chronic splenic anaemia. The cells of the spleen contain a proteolytic enzyme, but of its bearing on pathology nothing is known except that it may possibly assist in the autolysis of proteins in the spleen during starvation (Leathes). It has also been asserted that the spleen provides a substance which converts trypsinogen into trypsin (Herzen, Gachet and Pachon, Ciaccio and Pizzini), in opposition to Pawlow's well-known view that this is done by enterokinase.

II. SPECIAL PATHOLOGY AND DISEASES

Malformations.

Atrophy.

Post-mortem changes.

Wandering spleen.

Capsulitis.

Chronic venous engorgement.

Haemorrhages.

Infarcts.

Abscess.

Tuberculosis.

Syphilis.

Rickets.

Lardaceous disease.

Cysts.

New growth, non-malignant.

„ malignant, primary.

„ „ secondary.

Malformations.—Under this heading reference may conveniently be made to anatomical abnormalities in conformation, including the presence of accessory spleens, and to some changes in the position of the organ.

Very considerable physiological variation may exist in the outline of the organ; sometimes it is elongated and resembles the form met with in some animals: at other times it is more compressed and rounded than usual. The outline of the anterior margin may shew a number of notches which, in enlargement of the organ, may become much

accentuated ; occasionally a deep notch may even partially divide the spleen into two. Dr. A. Latham has shewn me a most remarkable abnormality of the spleen found in the post-mortem room of St. George's Hospital. The spleen gave off a long process which was bound down to the posterior abdominal wall by the peritoneum and ran down into the left side of the scrotum. In thickness it was equal to the little finger. Microscopically it was composed of splenic tissue. It was probably carried down in the descent of the testis, just as accessory suprarenals may be transported into the neighbourhood of the epididymis.

Accessory spleens or splenunculi are common ; they occur in the folds of peritoneum passing to the spleen, in the great omentum on the left side, and even between the layers of the costo-colic fold of peritoneum or suspensory ligament of the spleen. Usually they are close to the hilum of the spleen, and are not more than one, two, or three in number ; but as many as thirty or forty have been found. It is generally thought that accessory spleens are commoner in early life. Jolly, in eighty autopsies on patients under sixteen years of age, found them in twenty, or one in four ; but they became more frequent as age advanced. It may be that though more manifest in children they are not really more frequent. It has been stated that accessory spleens are commoner in the south of Europe than in the north. Especially in cases of transposition of the viscera, the spleen may be represented by a number of splenunculi, which may be clustered together like a bunch of grapes or be more widely separated.

The existence of these accessory spleens admits of two explanations : some of them, those in the hilum of the organ, are probably separated from the main body of the organ, a projecting tongue becoming pedunculated, and, finally, connected by blood-vessels only ; others, those in the great omentum, may with probability be regarded, like suprarenal "rests," as isolated and outlying fragments of the mesoblastic tissues destined to form the main organ. Like other "rests," they may become indented and embedded in other organs ; thus Biggs has described an accessory spleen in the tail of the pancreas. If accessory spleens become indented on the surface, and subsequently embedded in the substance of the spleen, they may form encapsuled tumours in the organ. Since the left lobe of the liver and the spleen are in contact in fetal life, it might naturally be expected that an accessory spleen might become indented and implanted in the surface of the liver ; this does not appear to have been observed, though as long ago as 1828 Bérard suggested that angiomas of the liver were encysted splenic "rests."

They undergo the same changes as the main organ. If in splenectomy an accessory spleen is left, it may by compensatory hypertrophy have some share in preventing the symptoms that occasionally follow removal of the organ.

Congenital absence of the spleen is very rare in bodies otherwise normal ; it has been noted in monsters. Dr. Garrod, in a paper on the

association of cardiac malformations with other congenital defects, refers to two cases of congenital *morbus cordis* in which the spleen was entirely absent ; in two other cases it was multiple, there being nine and four spleens respectively. In a case of absence of the spleen lymphatic hyperplasia elsewhere has been described (Hodenpyl).

In complete *situs transversus* the spleen is present on the right side of the abdomen. In congenital or in traumatic diaphragmatic hernia the spleen readily passes into the left pleural cavity. Out of 330 cases of diaphragmatic hernia tabulated by Rochard the spleen was in the hernia in 78 cases.

Atrophy.—In old people the spleen, like other lymphoid tissues, undergoes atrophy, sometimes to an extreme degree ; so that instead of its normal weight of 7 oz. it weighs only a few drams. The same condition of atrophy occurs in some cases of very chronic disease.

The capsule is shrivelled, thrown into folds, and somewhat opaque ; the substance of the organ is soft and pale ; and from atrophy of the pulp the vessels and trabeculae stand up prominently. In cases of simple atrophy there is no increase of pigment, but, if there has been any disease giving rise to extensive haemolysis, the substance of the organ may be deeply pigmented. Microscopically there is atrophy of the Malpighian bodies and of the pulp of the spleen, whilst the arteries shew arteriosclerosis. A rather firm fibrotic form of atrophied spleen is said to be associated with arteriosclerosis in the aged. This form of atrophy occurring in senile and marasmic conditions may be spoken of as simple.

There are cases, however, in which, although increased in bulk and weight, the spleen shews a replacement of its essential elements—the pulp and Malpighian bodies—by fibrous tissue. Such a change occurs in splenic anaemia and in chronic lymphadenoma—conditions probably due to chronic toxæmia or infection. The spleen cannot, in ordinary parlance, be said to be atrophied, but functionally it is much in the position of an atrophied organ. In this connexion Pilliet's (25) experiments are of considerable interest. He found that on dogs poisoned by metatoluenediamine, paraphenylen, and nitrite of sodium the Malpighian bodies became atrophied, and the splenic pulp distended with blood ; these changes he regards as characteristic of the senile spleen.

Post-mortem Changes.—Two very evident alterations which occur after death may be referred to.

(i.) When the stomach or colon contains much flatus, the surface of the spleen in contact with them is often found to be of a black or purple-green colour. The change is not present throughout the organ as it is in melanaæmia, but it is limited to the areas of contact with the hollow viscera, and on section is seen to be quite superficial. A similar appearance may often be found on the surface of the liver. It is due to gases, among which is sulphuretted hydrogen, diffusing through the walls of the stomach and intestines after death, and meeting in the spleen with traces

of iron contained in haemosiderin, and derived from haemoglobin ; as a result of this reaction sulphide of iron is produced.

(ii.) Occasionally the spleen is found honeycombed by small gas-containing cysts. This emphysematous condition is due to the activity of the *Bacillus aerogenes capsulatus*, and is a post-mortem or agony phenomenon.

Wandering Spleen.—The spleen, like the liver, is a floating organ tethered by peritoneal ligaments and moving with the diaphragm and in response to variations in the size of the hollow abdominal viscera. The spleen may be displaced by thoracic conditions or, in rare cases, by extensive deformity of the spine, but is not unduly movable in these circumstances. The name wandering spleen is applied to the organ when it is unduly movable.

Etiology.—The condition is most commonly seen in women with visceroptosis and in those who have borne children. It may be secondary to a movable left kidney, as this condition impairs the support of the spleen. Sometimes, however, there is no other evidence of visceroptosis. It is a rare condition, and is not often seen even in visceroptosis ; Dr. Keith estimates that it occurs in 2 per cent only of the cases of visceroptosis (*vide Vol. III. p. 869*). It may come on gradually, as the result of the alteration of intra-abdominal pressure after parturition, or less often appear suddenly after a blow on the left side. Normally, the spleen is supported in position by a ligamentous fold of peritoneum running from the splenic flexure of the colon to the diaphragm,—the phrenico-colic ligament or sustentaculum lienis,—and is also tethered to the left kidney and cardiac end of the stomach by the lienorenal and gastrosplenic folds of peritoneum. If from the shock of a blow or from gradual enlargement the spleen slips off the supporting ledge, provided by the phrenico-colic fold of peritoneum, it drags on its two other peritoneal ligaments, which may thus be elongated. Enlargement of the organ, especially the ague-cake spleen of malaria, is usually regarded as a factor in the production of the condition. But it is very rare to find the huge spleens of leukaemia movable. Congenital looseness of the ligaments has been thought to explain some cases, especially as the condition has been met with in several members of the same family.

Morbid Anatomy.—The spleen is usually enlarged ; this may depend on pre-existing morbid change, as in malaria, but is more commonly due to engorgement secondary to the mobility of the organ. The peritoneal pedicle of the wandering spleen, which may be a foot long, readily becomes twisted, and, as the thin-walled vein is more readily compressed than the resistant artery, intense engorgement results ; this is well shewn by the rapid diminution in size seen when the twist is unravelled at an operation. Considerable engorgement of the wandering spleen may occur without any twist of the pedicle. As the result of chronic engorgement the vessels shew obliterative changes and thrombosis which lead to fibrotic atrophy of the splenic tissue ; this, by necessitating gradual compensatory changes in the lymphoid tissue elsewhere, has been thought

to explain the absence of symptoms after splenectomy in such cases. The tail of the pancreas may be drawn into the pedicle of the wandering spleen, and has thus been partially removed in splenectomy.

Symptoms.—In some cases a wandering spleen is detected in the course of routine examination of a patient without any of the usual symptoms. The organ, which may rapidly alter its position in the abdomen, is commonly found in the left iliac fossa, less often in the umbilical region or right iliac fossa, in diaphragmatic, and in very rare instances in umbilical or inguinal hernial sacs. It may vary in size very considerably from alterations in the quantity of blood imprisoned in the organ. The patient may complain of a feeling of dragging and weight, or of discomfort in the back and abdomen. By dragging on the stomach it may interfere with digestion, or produce gastritis, dyspepsia, vomiting, and attacks of abdominal pain. As the result of traction on the duodenum, kinking of the common bile-duct and jaundice may be brought about (Treves). The chief symptoms, however, are those due to complications.

Complications.—As already mentioned the pedicle may become twisted; as many as six twists have been recorded (Stone). The symptoms thus produced are, like those of an ovarian cyst with a twisted pedicle, extremely severe and are those of acute peritonism. The twist may induce thrombosis in the splenic vein or even necrosis of the organ, which may set up peritonitis. The intensely distended organ may rupture on comparatively slight provocation. As the result of perisplenitis the organ may become fixed, and in some cases the symptoms have then disappeared. On the other hand, a wandering spleen may, when fixed in an abnormal position, give rise to dangerous symptoms and great difficulties in diagnosis; thus, a displaced spleen adherent in the pelvis may obstruct labour and imitate a solid ovarian tumour. Adhesions in connexion with a wandering spleen have been known to cause strangulation of the intestine.

Diagnosis.—The absence of the normal splenic dulness and the presence of a movable tumour with a notch, which can be returned to the normal position of the spleen, make the diagnosis clear. When the spleen has become fixed, it may be very difficult to come to a correct conclusion. It has been mistaken for an ovarian tumour, ectopic gestation, a fibromyoma of the uterus, a movable kidney, faecal accumulation, and a pelvic abscess.

The treatment is almost entirely surgical, as a pad or belt often fails to keep the organ in place. It has been suggested that the size of the spleen should be reduced by α -rays, and that a pad may then be sufficient to keep the organ in proper position (Murray). The surgical treatment consists in either splenopexy or splenectomy. The operation of splenectomy in these cases is attended with but a small mortality; out of 43 cases of splenectomy for wandering spleen, collected from literature in the decade 1890-1900, there were 3 deaths only (Warren).

Capsulitis is a convenient and comprehensive term for a group of

pathological changes which are of but little clinical importance, though pain in the left side and stitch may be explained by their presence. Under this heading we may include (i.) adhesions, the result of some past attack of peritonitis, local or general; (ii.) chronic inflammation of the whole or greater part of the peritoneal covering of the organ; and (iii.) the local thickenings, or lamellar fibromas, so common on the surface of the organ.

(i.) *Adhesions* round the spleen uniting it to the diaphragm, abdominal wall, stomach, or colon, may follow a past attack of acute peritonitis. These adhesions are vascular, and, of course, vary in their extent and firmness. Sometimes they may be filamentous and easily broken down; they may, in fact, become torn across as the result of abdominal movements, and then appear as small loose tags on the surface of the organ. I have seen fatal intraperitoneal haemorrhage result from traumatic rupture of vascular adhesions around the spleen in compensated hepatic cirrhosis. Occasionally they are so small at their point of attachment to the surface of the spleen as at first sight to resemble miliary tubercles. In other cases the adhesions may be so firm as to suggest recurrent attacks of inflammation or a prolonged inflammatory condition.

Very frequently local adhesions around the spleen are present without any other signs of past inflammation of the peritoneum. In such cases it will frequently be found that there are firm adhesions at the base of the left lung; presumably a past pleurisy or pneumonia had given rise to an inflammation of the diaphragm and of the peritoneum around the spleen.

In other cases local adhesions may be due to some cause originating within the spleen itself. The infarcts so frequently met with in the enlarged spleen of leukaemia often set up local peritonitis. The same thing occurs with infarcts secondary to endocarditis. Similarly, tuberculosis or lymphadenoma, or the enlargement and attacks of congestion of an ague-cake spleen, may be the cause of local peritonitic adhesions. Mr. Henry Morris has told me of several cases operated upon by himself in which on freeing peritoneal adhesions around the spleen a remarkable and rapid diminution in its size had taken place. In such cases the adhesions first became organised when the spleen was enlarged, and as the result of the permanent traction exerted by them the organ was held open and unable to contract.

(ii.) *Chronic peritonitis* attacking the whole or the greater surface of the organ is generally but a part of general chronic peritonitis (compare art. "Perihepatitis," p. 166). Chronic capsulitis or perisplenitis may, however, be independent of this general cause, and be due to some local lesion of the spleen, such as a cyst.

The macroscopic appearances are very characteristic. The organ is tightly shrouded in a firm, opaque membrane of almost cartilaginous consistency. Often, but by no means always, this fibrous membrane can be peeled off, so as to expose the peritoneal surface of the spleen. The outer surface of this "false" membrane is fairly smooth, but not uniform,

for, scattered irregularly over it, there are round depressions resembling the impress of rain-spots on soft sand. Their presence can be best explained by supposing that, after the formation of this inflammatory tissue, cicatricial contraction took place, and that, as a result of the increased tension thus brought about, the membrane had ruptured, either at its weakest spots or where the tension was greatest. This condition of chronic capsulitis may be accompanied by adhesions to the adjacent parts, but they are often absent.

(iii.) *Localised thickenings on the peritoneal surface of the spleen* are one of the commonest post-mortem appearances. They closely resemble the thickenings sometimes seen over the apices of the lungs, and may be compared with the "milk-spots" so commonly present on the pericardium. They may be aptly described as corns due to attrition.

Their frequent occurrence on the capsule of the spleen is probably due to the rhythmic contractions of the organ. On section they are seen not to invade the substance of the spleen, but to stand up as distinct growths in the capsule. These elevations are of various dimensions, from that of a pin's head to half a crown, and are seen to thin off gradually at the edges. When of old standing they frequently undergo calcification. Microscopically they are composed of lamellated and well-formed fibrous tissue, and are described as lamellar or corneal fibromas. Sometimes they are adherent to the parietal peritoneum, just as the milk-spots on the surface of the heart are occasionally united by an organised fibrous tag to the parietal pericardium. But more often, like the cardiac milk-spots, they are free.

Chronic venous engorgement of the spleen, such as is often seen resulting from obstructive heart or lung disease, does not give rise to any noticeable enlargement of the organ, as might naturally perhaps be expected. The spleen is hard, firm, of a deep red or purple colour, and about the normal size or slightly enlarged. The capsule is generally somewhat thickened, there is usually an increase of the interstitial supporting tissue—interstitial splenitis—and the venous sinuses are dilated. In 56 cases of nutmeg liver, all from uncomplicated cases of non-infective heart disease, Dr. Kelynack found the average weight of the spleen to be 7.32 oz.; whilst in 84 cases of cirrhosis, 53 being males and 31 females, the average weight of the spleen was—males 14.25 oz., females 11.62 oz., or for both sexes together 12.93 oz. In thrombosis of the splenic vein the organ is greatly increased in size. I have seen it weigh 36 oz.

In portal cirrhosis of the liver the spleen is generally but by no means constantly heavier than normal. In 147 cases of cirrhosis, of which 73 were fatal from the direct effects of the disease, the remaining 74 dying from independent causes, the average weight of the spleen was 10 oz.; taking the normal weight as 7 oz., this shews an increase of 3 oz. In the 73 cases of fatal cirrhosis the average weight of the spleen was 11.5 oz., and in the 74 cases fatal from independent causes 9 oz.; so that the spleen is heavier in cases of active cirrhosis than

when this condition is latent. There did not appear to be any constant relation between the weight of the spleen and that of the liver. Dr. Price, however, in an analysis of cases of cirrhosis, found large livers and large spleens associated together.

In cirrhosis of the liver—in addition to mechanical venous obstruction, which, as shewn by cases of backward pressure due to cardiac or pulmonary disease, is not of itself sufficient to give rise to splenic enlargement—there is frequently a toxic condition of the blood. To this latter factor the splenic enlargement in cirrhosis is probably largely due, for it is most marked in the early stages of cirrhosis before the portal obstruction has become very excessive. It would appear more probable, therefore, that the splenic enlargement in portal cirrhosis is due to toxins setting up hyperplasia and inflammatory softening of the organ, so that it readily becomes over-distended with blood as the result of backward pressure. In favour of this is the observation that when any toxic or infective condition be added to mechanical congestion, the organ enlarges and becomes softened. This is well seen in infective endocarditis, in which the diffused enlarged condition of the organ contrasts with the cardiac spleen already described as resulting from high venous pressure alone.

Haemorrhages.—In an examination of 130 still-born children, Dr. H. Spencer found a large number of visceral haemorrhages in various organs, due apparently to damage received during delivery. The spleen shewed haemorrhages in three cases only ; which is perhaps accounted for by the small size, mobility, and extensibility of the organ. In later life, injuries may give rise to haemorrhages into the substance of the organ. Small haemorrhages into the pulp of the organ are commonly seen in bacterial infection. Occasionally large haemorrhages are found either into the substance or under the capsule of the spleen. It may be very difficult to determine the cause ; infective embolism should always be looked for ; possibly arteriosclerosis may, as in cerebral haemorrhage, be the responsible factor. I have seen a very large haemorrhage under the capsule of the spleen in an old man with extreme arteriosclerosis ; the onset of symptoms was sudden, and—like pancreatic haemorrhage—suggested perforative peritonitis.

Infarcts.—Clinically, infarcts of the spleen manifest themselves by pain and tenderness in the splenic region, chiefly due to the accompanying local peritonitis and imitating pleuritic pain, by some enlargement of the organ, and by a friction rub. Occasionally there may be sudden and severe pain, presumably at the time that the embolus becomes impacted in the vessel ; the temperature is subsequently raised.

Causes of Infarction.—Fragments of blood-clot or vegetations dislodged from the valves or endocardium of the heart are the most frequent source of embolism of the splenic artery. The same result may follow detachment of particles of calcareous material set free from sclerosed valves or from atheromatous patches in the aorta.

These emboli are divisible into two kinds—(i.) infective, those which

contain pyrogenic micro-organisms, such as are present in cases of infective endocarditis or, much more rarely, in infective arteritis. Such emboli give rise to suppurating infarcts, and the process is essentially the same as that of a pyaemic abscess in the organ; (ii.) simple or non-infective emboli which give rise mechanically to anaemia, necrosis, and the changes of a simple infarction.

Besides embolism there are other forms of interference with the circulation which may result in the production of an infarct. Thrombosis in the branches of the splenic artery may have this effect, as is commonly seen in the greatly enlarged spleens of leukaemia, sometimes in enteric fever, and in rare instances in polycythaemia with cyanosis (Hutchison and Miller). Occasionally thrombosis of the trunk of the splenic vein may give rise to multiple infarcts. In two instances that have come under my own observation, the resulting infarcts have been anaemic and not haemorrhagic. It might, perhaps, have naturally been expected that complete thrombosis of the splenic vein would have led to a haemorrhagic infarct, as in Litten's experiment of ligature of the renal vein.

Morbid Anatomy of a Splenic Infarct.—The terminal branches of the splenic artery do not anastomose with each other except by capillaries; each of them supplies exclusively a definite area of the spleen, they are therefore called end-arteries. When one of these terminal branches has been recently blocked by a simple non-infective embolus, the area of the spleen supplied by it becomes anaemic, and the condition is a white or anaemic infarct. This is what is commonly seen in the spleen; but occasionally this condition of anaemia becomes succeeded by one in which the area is full of blood, a red or haemorrhagic infarct. The affected area is roughly conical, the apex being towards the hilum of the organ, and corresponding to the occluded artery, and the base towards the capsule. A thin area of healthy splenic tissue can usually, however, be seen immediately under the capsule which, together with the capsule itself, is nourished by the capsular arteries of the organ.

The anaemia is succeeded by coagulation necrosis; the affected area becomes somewhat swollen or infarcted, projects slightly above the surrounding surface of the organ, and is of a dull white colour. If a recent white infarct is compared with the whitish-yellow scar left by an old infarct, it will be seen that the cicatrisation and contraction of the old infarct have led to a depression; whilst the recent infarct is on a level with or even projects above the surrounding surface.

When an anaemic becomes a haemorrhagic infarct the blood first distends the vessels, which, however, from malnutrition are unable to contain it, and allow it to deluge the affected area. This engorgement of the vessels Cohnheim regarded as due to a regurgitation of blood from the veins of the adjacent areas, which, unlike the arteries, do anastomose. Litten's experiments, however, pointed strongly to the blood being derived from the arteries running in the capsule of the organ and not from the veins.

Following on coagulation necrosis and its accompanying fatty degenera-

tion, inflammation is set up around the infarction. This is shewn by a zone of congestion in the substance of the organ, and by local peritonitis on the surface. This inflammation leads to an invasion of the infarcted area by young connective-tissue cells, phagocytes, and so forth; and the processes of replacement fibrosis and absorption of the necrosed tissue take place side by side. Absorption of an aseptic infarct is said to be due to autolysis or self-digestion by intracellular ferment (proteases) liberated from the dead cells. In large infarcts the centre is softened by autolysis while the margins remain firm (H. G. Wells). Eventually a depressed cicatrix is left, with perhaps in the centre, if the infarct be large, some encapsulated caseous debris, the remains of necrosed tissue which was too extensive to be absorbed. Occasionally calcification of the cicatrix of the infarct may occur.

The local peritonitis may produce loose tags of fibrous tissue, or adhesions to adjacent organs, to the omenta or to the diaphragm.

When an infective embolus lodges in the spleen, the first stages are the same as those described above for a simple embolus; and sometimes in infective endocarditis a definite anaemic infarct may be seen before the subsequent acute inflammation and suppuration have supervened. This soon passes into a pyaemic abscess.

Abscess.—The softened and often diffused condition of the spleen seen in cases of bacterial infection may be described as a splenitis, and is in some degree comparable to lymphadenitis. This condition of the spleen, commonly seen in infectious fevers, very rarely indeed goes on to suppuration in these diseases.

One of the most frequent causes of splenic abscess is infective endocarditis. In this disease the spleen is enlarged and softened, in short, in the condition seen in bacterial infection. When an abscess occurs it is the result of embolism in the organ, giving rise first to an infarct which, instead of running the course of an ordinary infarct, breaks down, and suppurates by reason of the micro-organisms contained in the embolus. Such an infarct in the earliest stages may be anaemic or haemorrhagic, but softening and suppuration soon supervene. As the result of union of two or more such suppurating infarcts the whole spleen may become converted into an abscess cavity.

In pyaemia, abscesses embolic in origin, like those in infective endocarditis, are often met with. Thus, in 430 cases of general pyaemia abscesses were found in the spleen in 39 (S. Paget).

In pylephlebitis abscesses may form in the spleen, but this is very rare as compared with splenic abscesses in general pyaemia. Dr. S. Phillips found three abscesses in a spleen weighing 38 oz.; the suppurative phlebitis of the portal vein was due to perforation of a mesenteric vein by a bristle. In suppurative pylephlebitis the abscesses in the spleen are not necessarily always due to the direct spread of the inflammatory process along the splenic vein, but may be due to general pyaemia.

Suppuration in the spleen has, in rare instances, occurred in enteric

fever ; it has been shewn to be due to the activity of the typhoid bacillus, but may be due to secondary infection with other micro-organisms. Infarcts, as mentioned above, are found very occasionally in typhoid fever ; they may slough, and thus give rise to an abscess. Splenic abscess may occur in malaria from secondary infection by pyogenetic micro-organisms.

Extension of inflammation from adjacent parts usually only sets up peritonitis on the surface of the spleen ; but a perforating ulcer in the stomach or colon may penetrate the spleen, and give rise to suppuration in the organ. Hydatid cysts of the spleen are rare ; if suppuration occurred in a cyst embedded in the organ it would closely resemble a splenic abscess. A softening gumma, and perhaps actinomycosis, may give rise to the appearances of an abscess in the spleen.

Injury has been the only discoverable antecedent of some splenic abscesses ; it probably acts by reducing the resisting power of the organ, and so giving free play to any pyogenetic micro-organisms present. A number of cases have been described in which no definite cause for splenic abscess was forthcoming ; some of these cases were probably pyaemic and embolic in origin, and secondary to suppuration elsewhere. Thus, like cerebral abscess, suppuration in the spleen may be secondary to inflammation and suppuration in the thorax.

Symptoms.—In most cases suppuration is found in the spleen as a complication of some other disease, especially of infective endocarditis. When abscess in the spleen is not subordinate to some other disease the symptoms are those of fever with local peritonitis, and enlargement and tenderness of the organ. The abscess may burst into the peritoneal cavity, the hollow viscera, the pleura, or the lung. Small abscesses in the substance of the spleen may be latent.

The treatment is surgical.

Tuberculosis.—In *generalised tuberculosis* the spleen almost always shews miliary tubercles. They are much more evident on the capsule than in the substance of the organ, where there is, moreover, some difficulty of distinguishing them by the naked eye from Malpighian bodies. On the surface they appear as grey, rarely as yellow points ; occasionally they may set up local peritonitis, and may even give rise to the formation of a fibrinous membrane on the surface of the organ. In *generalised tuberculosis* the spleen is enlarged and soft ; when of rather older date, the tubercles may caseate while still remaining discrete.

Chronic Tuberculosis.—Large caseous masses, though common in the spleens of animals, are by no means common in man ; when they do occur, they are more often met with in children than in adults. Tuberculous foci, however, grow more readily in the spleen than in the liver. Large, round, caseous masses, with some smaller miliary tubercles near them, are embedded in the spleen substance, against which they shew up in a striking manner. After a time they soften down in the centre, and can then be recognised at once. Caseating tuberculous material, before it has softened down, cuts with a firm section, and to the naked eye so

closely resembles the "hard-bake" spleen of chronic or hard lymphadenoma that a microscopic examination may be required to distinguish between them. The caseous masses are not, as a rule, surrounded by fibrous tissue; but in cases of exceptional chronicity the spleen may be extensively fibrosed, and so pigmented as to resemble lymphadenoma. Calcification may occur in the caseous tuberculous patches.

In *primary massive tuberculosis* the spleen is greatly enlarged and more extensively tuberculous than any other organ in the body. The tuberculous lesions may be (i.) miliary, (ii.) necrotic and haemorrhagic, or (iii.) fibro-caseous, the commoner form, which resembles multiple new growths or infarcts.

Clinically, the enlarged spleen may be the only organ affected and present as a notable abdominal tumour, or the liver may also be enlarged, or the spleen, liver, and lymphatic glands may all be palpably enlarged. In a few of the nine cases collected by Collet and Gallavardin there was polycythaemia with or without cyanosis. In a case with a red count of 8,200,000 there was no cyanosis (Moutard-Martin and Lefas). Clinically, primary massive tuberculosis of the spleen may closely resemble chronic splenic anaemia of adults, and in rare cases chronic polycythaemia with cyanosis and enlarged spleen. Injection with tuberculin would assist in the diagnosis. Splenectomy has given good results in some cases.

Syphilis.—*Acquired Syphilis.*—During the exanthem the spleen is often found to be enlarged; this may be associated with anaemia and fever.

In the tertiary stage gumma is rarely met with; Prof. Still has only been able to collect twenty recorded cases. When present, they may reach a very large size; thus, in a case recorded by Prof. Delépine and Dr. Sisley, one-third of the spleen, which, though it was not lardaceous, weighed 38 oz., was occupied by a large gumma; numerous smaller gummas were present, and there was general fibrosis of the organ. Over a gumma capsulitis and adhesions to the diaphragm and adjacent parts are found, especially if it impinges on the surface. Apart from gummas, capsulitis and cicatrices are often found in the bodies of syphilitic subjects.

As a consequence of syphilis lardaceous change in the spleen often results.

In *congenital syphilis* the spleen is generally enlarged, and firmer than normal; sometimes the splenic enlargement is excessive, and may be associated with hepatic enlargement. Dr. Gee, who first drew attention to this form of splenomegaly, found enlargement in one-fourth of all cases of hereditary syphilis, but recent estimates are considerably higher (Still 45 per cent, Colcott Fox and Ball 48 per cent, Marfan 50 per cent, and Coutts 63 per cent). Hereditary syphilis is probably the commonest cause of infantile splenomegaly; thus, in 40 infants, under two years of age, with splenomegaly there was a syphilitic taint in 31 or 77.5 per cent (Marfan); in 348 children, under twelve years of age, with splenomegaly syphilis was present in 147, or 42.2 per cent (Carpenter). According to Birch-Hirschfeld, Lower, Ruger, and Parrot the spleen in syphilitic

infants weighs 30 to 38 grams (1 to $1\frac{1}{4}$ oz.) instead of the normal 9 grams ($2\frac{1}{2}$ drams), but rapidly diminishes in size, and at the forty-fifth day of life weighs about 21 grams (5 drams). Structurally, there is considerable congestion at first; later "myeloid transformation," as shewn by the presence of nucleated red blood-corpuscles and myelocytes, is described (Paris and Salomon). Evidence of haemolysis was found by Potier. Eventually there is diffuse fibrosis, which may lead to atrophy.

Lardaceous disease may occur as in acquired syphilis. Gummas appear to be very rare, rarer perhaps than is usually thought; Prof. Still was only able to collect six cases in children. Of these, four occurred in late hereditary syphilis between the ages of six and eleven years, and the other two in early infancy. In four of the cases there were gummas in the liver, and in a fifth in the kidney. In none of the cases was there a solitary gumma in the spleen; usually they were numerous, and in three miliary.

Rickets.—It is generally recognised that rickety children may have a palpable spleen, but the importance of rickets as a cause of splenomegaly has been rather variously estimated. Dr. Hutchison estimates that the spleen is not appreciably enlarged in more than 5 per cent of rickets, and Drs. Cowan and M'Clure found the spleen enlarged in 17 or 4·07 per cent of 417 cases of rickets. Dr. Colcott Fox and Dr. Ball estimated that the spleen might be enlarged in perhaps 25 per cent of the cases of rickets. It is, however, probable that rickets does not itself give rise to splenomegaly, but that some additional and commonly combined factor, such as syphilis or other infection often intestinal in origin, is the causal agent. The enlargement may in some cases be apparent rather than real, and due to downward displacement of the organ as the result of rickety deformity of the thorax. The spleen may shew some fibrosis.

Lardaceous Disease.—The spleen seems to be the organ most frequently attacked; the combined statistics of Birch-Hirschfeld, Loomis, Dickinson, Goodhart, and Turner give 795 cases of lardaceous disease, in which the spleen was affected 585 times, the kidneys 539 times, and the liver 387 times. Lardaceous disease attacks the spleen in two ways:—

(i.) The "sago" spleen; the capillaries of the Malpighian bodies are the parts affected, the arteriole in the centre of the corpuscle being as a rule healthy. The Malpighian bodies are enlarged to three or four times their normal size, and, being translucent, to the naked eye resemble grains of sago. The pulp and the lymphoid cells are unaffected. The sago spleen is firm, somewhat anaemic, and increased in size.

(ii.) The diffuse, waxy spleen, uniformly lardaceous or bacony spleen. This is much less common than the sago spleen. The chief changes are in the walls of the blood sinuses, which become much thickened and swollen. The lining endothelium is not affected. The small arteries are affected, but the trabeculae remain unattacked. The Malpighian bodies are unaffected, or affected but rarely; they may be present, but more often they have disappeared. The splenic pulp becomes lardaceous

secondarily. The diffuse, waxy spleen is enlarged, and is heavier than the sago variety ; it is resistant, and presents a dry surface on section.

Cysts.—*Hydatid.*—The spleen is but seldom occupied by hydatid cysts ; according to Thomas, in only 2 per cent of cases of hydatid disease. In 45 cases it was the only seat of echinococcus cysts, and in 43 other cases collected by him other organs, in 37 cases the liver, were also infected. In half the cases of hydatid disease of the spleen no symptoms were noticed, and the cyst was only discovered after death. The contracted remains of spontaneously cured hydatid cysts are sometimes found.

Non-parasitic cysts of various kinds occur, but none of them are common. Dermoid cysts are so rare as to be pathological curiosities ; one is briefly mentioned by Andral. It is possible that when an ovarian embryoma ruptures and multiple implantation-cysts arise on the peritoneum that the spleen might thus be affected. Of the various forms of cysts described in the spleen some are quite small, may be multiple, and have serous contents ; in a few instances small serous cysts have been found in lardaceous spleens. Serous cysts may be due to lymphatic obstruction, to changes in lymphangiomas, or to infolding of the peritoneal endothelium, either before or after birth. Larger cysts may be serous, sero-sanguineous, or sanguineous ; the cyst is unilocular as a rule, but K. Thornton removed a multilocular cyst containing 30 oz. of blood-stained fluid and a large quantity of cholesterol. The usual explanation given for the sero-sanguineous or sanguineous cysts is traumatic haemorrhage either into the capsule or into the substance of the spleen. The cysts may not be noticed until long after the injury presumably responsible for the haemorrhage ; thus, in Credé's case ten years elapsed between the injury and the operation. It is said that in Arabs haemorrhagic cysts, due to ruptures restricted by surrounding perisplenic adhesions, are not uncommon (Brunswig-le-Bihan). Gross injury, however, is not the only cause of sanguineous cysts, probably arterial disease may give rise to splenic haemorrhage. In Powers's 31 cases there were 23 females, of whom 17 were in the menstrual period of life, and he concludes that child-birth and menstruation favour the formation of these cysts. Pilliet thought that degenerative changes in naevi might give rise to cysts. Sanguineous cysts are less rare than the serous variety ; Bryan collected 22 examples of sanguineous and 9 of serous cysts.

The cyst may contain large quantities, even 20 pints, of recent or old blood, and by pressure give rise to dyspepsia and constipation. There may be sudden exacerbations with increase in the size of the cyst, probably from fresh haemorrhage ; these attacks may be induced by very slight causes. The cysts commonly set up some local peritonitis with the production of perisplenic adhesions. Rupture into the peritoneal cavity may occur. Diagnosis is difficult on account of the rarity of the condition ; a history of injury is important, though this may also precede the onset of a pancreatic cyst. Other conditions which may resemble it are an enlarged or wandering spleen, and hydatid, omental, or ovarian cysts.

The distinction from hydronephrosis and large cysts of the left kidney depends on the absence of colon resonance in front of renal tumours, and on the absence of other characteristics of hydronephrotic enlargements. The cyst should not be tapped, as this procedure is not free from risk, but the abdomen should be opened and the cyst incised and drained, or the spleen removed, as may seem most desirable.

New Growth, Non-Malignant.—*Angiomas* are very rare. A few cavernous angiomas have been described ; they may undergo fibrous change (Lubarsch). Small multiple angiomas in the spleen, giving the organ the appearance of a granular kidney with cysts, were found in a case with numerous angiomas elsewhere in the body, one in the spinal canal having become sarcomatous (Devic and Tolot). In some instances in which the spleen is occupied by an angiomatous growth in common with other organs, it may be difficult to be sure whether the growth should be classified as a simple angioma or as an angiosarcoma. As already mentioned, some cysts of the spleen have been thought to be due to degenerative changes in angiomas. A few isolated examples of *Lymphangioma* have been recorded.

Malignant Growths.—*Primary*.—Although a good many of the cases described as primary carcinoma of the spleen were in reality examples of the form of chronic splenic anaemia of adults originally described by Gaucher as *l'epitheliome primitif de la rate*, and now recognised as a distinct variety of chronic splenic anaemia (the Gaucher type, Brill), there is no doubt that primary malignant disease in the form of sarcoma, angiosarcoma, or endothelioma does arise in the spleen. Picou and Ramond described a primary carcinoma of the spleen, for which they adopted Birch-Hirschfeld's suggestion that it was derived from pancreatic cells included in the spleen in fetal life. This hypothesis provides a reasonable explanation of a splenic tumour thought to be a primary carcinoma, but it cannot be said that the occurrence of such a tumour has been established ; Picou and Ramond's case manifestly belonged to the form of splenic anaemia mentioned above. It must, however, be admitted that the chronic endothelial proliferation in the Gaucher form of splenic anaemia presents microscopical appearances suggesting that the benign hyperplasia may pass into a sarcomatous growth. Prof. Osler speaks of these cases as chronic endothelioma, Stengel regards the Gaucher type of chronic splenic anaemia as a neoplasm somewhat comparable to diffuse myeloma, and Bunting has made a careful study of the relation between the Gaucher type and primary sarcoma.

Primary sarcoma of the spleen is rare ; it may be lymphosarcoma, round-celled, irregular-celled sarcoma, angiosarcoma, or fibrosarcoma, and may be haemorrhagic. The malignant nature of the tumours has been definitely shewn in several instances by metastases and by invasion of adjacent tissues.

The clinical aspect of the cases consists mainly in the presence of a splenic tumour ; if irregularities can be felt on the surface of the spleen there is good ground for deciding that it is not chronic splenic anaemia,

which has often been described as primary malignant disease of the organ. Jepson and Albert have tabulated 32 cases (some of which are doubtful) as primary sarcoma of the spleen; of these 12 were submitted to operation, 11 to splenectomy, and 1 to enucleation of the growth: of 8 cases that survived the immediate effects of the operation 3 died from recurrence.

Secondary growths are by no means frequent in the spleen, and when the organ is implicated it is more often by continuity than by haemic infection. Thus, in 735 autopsies of carcinoma of the mamma the spleen was the site of secondary growths in 17 cases; and in 244 cases of cancer of the uterus there was only one case in which a secondary nodule was found in the spleen (S. Paget). In 677 cases of carcinoma and sarcoma at Guy's Hospital the spleen was affected in 23, but in 16 of these 23 the spleen was directly invaded from the stomach, pancreas, or peritoneum, so that a true metastasis occurred in 7 only (Taylor).

In fifty cases of melanotic sarcoma quoted by von Ziemssen the spleen contained secondary growths in thirteen.

For spleen in *malaria*, *lymphadenoma*, *splenic anaemia*, and *leukaemia* the reader is referred to the special articles on those subjects.

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LYMPHADENOMA

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SYNOMYS.—*Hodgkin's Disease*, *Lymphadenosis*, *Adenoid Disease* (Southey), *Anaemia lymphatica* (Wilks), *Lymphatic cachexia* (Mursick), *Lymphosarcoma* (Virchow), *Lymphoma*, *Lymphosarcomatosis*, *Lymphoma malignum* (Billroth), *Adénie* (Trousseau), *Lymphadénie* (Ranvier), *Cacherie sans leucémie* (Bonfils), *Pseudoleukämie*.

Short Description.—Lymphadenoma is characterised by a general and progressive enlargement of one or more groups of lymphatic glands, frequently accompanied by enlargement of the spleen and anaemia. The enlargement of the lymphatic glands is due to the development of lymphoid tissue with a definite and characteristic structure. Disseminated growths may arise in various organs, but more especially in the spleen, liver, kidneys, and alimentary canal. In the blood the red corpuscles may be diminished in number and deficient in haemoglobin, and in some

cases there is an increase in the number of the leucocytes ; the blood changes, however, are not characteristic.

History.—The earliest description of the general enlargement of the lymphatic glands, together with the presence of nodules in the spleen, was given by Malpighi in 1669 ; but apparently he did not consider that the combination of these two morbid conditions constituted a definite disease. Craigie, in 1828, defined the anatomical characters of the glandular enlargements, and pointed out how they differed from those of "scrofulous" enlargement and from those of cancer of the glands. To Hodgkin rightly belongs the credit of having first described, in 1832, the main clinical features of the disease which now bears his name. He described the association of the enlargement of several or of many lymphatic glands with changes in the spleen as an important characteristic of the disease. Velpeau, in 1839, described the enlargement of the lymphatic glands which was not associated with scrofula. In 1856 Sir Samuel Wilks drew attention to some cases and to their similarity to those described by Hodgkin twenty-four years before. In the same year Bonfils recorded a case of *hypertrophie ganglionnaire générale, cachexie sans leucémie*, with an account of the necropsy, and gave a clear description of the characters of the disease. In 1858 Billroth described the structure of the enlarged glands, and Wunderlich published 2 cases. The following year further contributions to the subject were made by Dr. Pavy and by Cossy. Virchow gave a short description of the disease in 1864. In 1865 Sir S. Wilks gave a further description of his cases and of the general characters of the malady. Cornil collected the cases which had already been observed, and recorded 2 others with a careful account of their pathological anatomy. The same year Troussseau devoted a chapter in his *Clinique médicale* to a description of the characters and nature of the disease, to which he gave the name of *adénie*. In 1866 Wunderlich gave the first thorough account of the disease in German. The year following, Müller described 7 additional cases from Niemeyer's clinic. In 1870 Murchison related the history of the symptoms of the malady, and gave the results of Burdon-Sanderson's microscopical examination of the diseased organs. The disease was described as pseudo-leukaemia by Mosler in 1878. Hodgkin's disease was discussed at the Pathological Society of London in 1878, and a most comprehensive account of it was given by Sir W. Gowers in 1879. In 1892 Dreschfeld published a clinical lecture on acute Hodgkin's disease, with observations upon the condition of the blood. During the next ten years several observers described cases in which lymphadenoma was associated with tuberculosis. Sternberg found tuberculosis in 8 out of 13 autopsies on cases of Hodgkin's disease. This association suggested that lymphadenoma was probably a form of tuberculosis. Further investigations, however, shewed that this view was untenable, and that, although the two diseases sometimes occur together, or lymphadenomatous glands may become infected with tubercle bacilli, they are nevertheless perfectly distinct. At the annual meeting of the British Medical Association held at Cheltenham in 1901, an important

discussion on lymphadenoma was opened by Dr. Michell Clarke, who gave a comprehensive account of the disease, and maintained that there was no satisfactory evidence that lymphadenoma was a lymphatic tuberculosis. In 1902 a discussion on "lymphadenoma in its relation to tuberculosis" took place at a meeting of the Pathological Society of London, as a contribution to which Dr. F. W. Andrewes gave a comprehensive account of the minute structure of the glands in lymphadenoma. The same year Reed came to the conclusion that Hodgkin's disease is a distinct clinical and pathological entity, the growth presenting special histological features which are characteristic of the disease, the cause of which is as yet undiscovered.

Etiology.—Our knowledge of the etiology of lymphadenoma is very scanty. Of the immediate causes we know nothing definite as yet. By some physicians it is supposed to be due to a micro-organism; and the course of acute forms of the disease is highly suggestive of an acute infective process. The present state of our knowledge of this part of the subject will be considered more fully in dealing with the pathology of the disease. When we examine the circumstances in which the disease arises we find that in more than half of the recorded cases none of the remoter causes can be traced. Thus, Sir W. Gowers found that in 64 out of 114 cases the patients were in good health up to the beginning of the disease, and no etiological factor could be discovered to account for the onset. In some cases, however, there are certain antecedents which appear to be concerned in the event, and to these I shall now refer.

Heredity.—Evidence of direct transmission from parent to child is almost entirely wanting. Müller recorded one case in which all the children of a father who suffered from lymphadenoma were subject to enlargement of the lymphatic glands. The disease is not prone to occur in the more distant blood relations of the patient. Tuberculosis is the only disease which appears to cause any proclivity to it, and, whether as pulmonary phthisis or as tuberculous disease of the lymphatic glands, may be found in one or more members of the same family. But when we consider the great frequency of tuberculosis we cannot assume that such cases are more than coincidences.

Sex.—The male sex is much more liable to the disease than the female; it occurs three times as often in men as in women: thus, 75 per cent of Sir W. Gowers' cases were males, as were also 40 out of 58 cases in Mr. J. Hutchinson's tables quoted by Prof. Osler.

Age.—Although no period of life is exempt, it occurs most frequently in early and late adult life, from twenty to forty and from fifty to sixty; in middle life, from forty to fifty, it is comparatively uncommon.

Locality.—The disease occurs independently of any special local conditions, and there is no evidence that any one kind of climate specially favours its occurrence.

Personal Antecedents.—Tuberculosis.—Tuberculous disease of the lymphatic glands may dispose them to a later development of lymph-

adenoma ; for in a few cases the onset of the disease has been preceded by "scrofulous" enlargement of the glands with suppuration.

Syphilis.—Three cases are mentioned by Sir W. Gowers in which the onset of the disease had been preceded by syphilis, but the relation of the one to the other is doubtful.

Parturition.—The disease rarely occurs during pregnancy, but several cases have occurred shortly after childbirth, and have run a very acute course, ending fatally within a few weeks. Parturition thus has an unfavourable influence upon the progress of the disease.

The onset has sometimes been preceded by exposure to cold. In a few instances want of food, excess of alcohol, over-exertion, and mental depression appear to have contributed somewhat to the initiation of the disease.

Local Irritation.—Trousseau pointed out that in some cases the enlargement of the lymphatic glands was, in the first place, due to some local source of irritation in the neighbourhood of those glands which first become affected. Thus, a local glandular enlargement, due to otorrhoea, chronic nasal catarrh, or a carious tooth, has been followed by the appearance of the disease in other glands. In other cases the disease has been preceded by an increase in the size of the respective glands in inflammation of the pharynx, inflammation of the lacrymal sac, and in soft chancre. This sequence is, however, very rare in comparison with the great frequency of glandular enlargement from local infection.

Morbid Anatomy.—The most important morbid changes are enlargement of lymphatic glands, enlargement of the spleen, and the presence of nodules of lymphadenoid growth in various organs of the body.

Lymphatic Glands.—The most striking feature of the morbid anatomy of lymphadenoma is the enlargement of the lymphatic glands. In health the lymphatic glands may be conveniently divided into primary, secondary, and tertiary groups. Of these the primary and secondary are always to be found, whereas the tertiary glands are usually so small that they may escape observation ; but they become enlarged in special circumstances. The inguinal glands are a primary group, the popliteal are secondary glands. Dr. Gulland states that in the axilla there are tertiary glands which ordinarily measure 1 or 2 millimetres only in diameter, but which in woman during lactation become temporarily enlarged. They afterwards disappear, as Mr. Stiles has found, by a process of fatty involution. These tertiary glands may also become enlarged if carcinoma develop in the mamma.

In lymphadenoma the extent of the lymphatic enlargement varies considerably in different cases. In some it is confined to a few groups of glands ; in others a large number are affected. The primary lymphatic glands are the most liable to be enlarged. The cervical glands are more frequently affected than any others ; after these in order of frequency come the axillary, inguinal, retroperitoneal, bronchial, mediastinal, and mesenteric glands. In addition to these, smaller groups of the secondary

glands are often affected along with the primary groups with which they are connected. Thus, with the inguinal the popliteal glands, and with the axillary the epitrochlear glands may be affected. Tertiary glands may also become affected, and thus large glands may be found along the line of lymphatic vessels in unusual situations ; as, for instance, beneath the pectoral muscle. The same set of glands is usually affected on both sides of the body, but the enlargement may be greater on one side than on the other, or may affect one side only. A single gland may become as large as a hen's egg, and a group may reach the size of a cocoa-nut. The enlarged glands are oval in shape, and movable in the earlier stages of the disease. Later, adjacent glands become firmly adherent either by the direct extension of the lymphadenoid growth from one gland to another, or by adhesive inflammation of the capsules of the glands and the surrounding tissues. The enlarged glands may be either soft or firm. The consistence does not depend upon their size, as both large and small glands may be either soft or hard. On section the colour is a greyish white, with red spots at the points where dilated vessels have been severed by the knife, or where haemorrhages have taken place. In some cases in which the glands are firm a considerable quantity of fibrous tissue can be seen on section. No degenerative changes are seen except when necrosis has occurred as the result of secondary infection of the diseased gland by the tubercle bacillus or some other micro-organism. When the cut surface of a soft gland is scraped, a juice is obtained which contains lymphocytes, larger endothelial cells which are often multinuclear, red corpuscles, and spindle-shaped cells from the walls of the vessels. The firm fibrous glands, when scraped, yield little or no juice.

In the neck the glands which lie above the clavicle are most frequently affected, and may reach a large size. The glands along the sterno-mastoid muscle, the submaxillary, and the suboccipital glands may be diseased. Chains of enlarged glands may also connect this group with the axillary or with the intrathoracic group of glands. Various secondary effects may be produced by enlargement of the cervical glands ; the larynx may be pushed to one side, the trachea may be narrowed, the internal jugular vein may be compressed and thrombosed, or the recurrent laryngeal nerve may be involved. The glands in the axilla are frequently affected, and may reach a large size. They are generally enlarged on both sides of the body, but to a greater extent on one side than the other.

In the thorax the anterior mediastinal glands are often found enlarged, and may form a mass extending the whole length of the pericardium. In some cases the growth extends into the region of the thymus or into the pericardium. Both the heart and the left lung may be pushed out of place by the enlarged glands. The bronchial glands often form large masses which may compress the bronchi to a considerable extent, and the growth may extend into the lung itself. When the glands of the posterior mediastinum are affected they rarely cause any compression of the aorta, oesophagus, or thoracic duct ; though in some cases the wall of the oesophagus or even the vertebrae may be invaded by the growth of the

glands. In the abdomen the glands most frequently affected are those which lie behind the peritoneum along the spine. The pelvic glands may also be enlarged and compress one of the ureters. Sir W. Gowers mentions one case, recorded by Bonfils, in which the lumbar and pelvic glands together weighed eight pounds. The mesenteric glands are seldom affected, and when diseased they do not reach any great size. In one of my cases there was jaundice at the time of death due to compression of the common bile-duct by a mass of enlarged glands. The inguinal glands are enlarged in about 50 per cent of the cases, and often form large masses in the groin, compressing both vessels and nerves in that region.

Microscopical Appearances.—A normal lymphatic gland consists of a reticulum upon which lie endothelial cells, the spaces of the network being filled in by numbers of lymphocytes. From examination of a large number of lymphatic glands of man and other animals, Dr. T. L. Bunting considers that the elements of the reticulum form a great part, if not the whole, of the trabeculae, and "its cells in places form patches of endothelium at the borders of the sinuses, and its cells are often phagocytes." In lymphadenoma characteristic changes are found in the lymphatic glands which can be distinguished from the pathological changes due to other diseases (Andrewes, Reed). In lymphadenoma the distinction between the cortex and medulla is much less marked in the affected than in normal glands. The lymphocytes are less numerous, and there is an overgrowth of the reticulum. The endothelial cells are increased in number, and some of them are enlarged, containing two, four, or more deeply staining nuclei. These large multinuclear, "lymphadenoma cells," which were described by Virchow, are very characteristic of the disease. They are both smaller and rounder than the giant cells of tuberculosis, and contain fewer but larger and more centrally placed nuclei. Mitoses may frequently be seen in them. Eosinophil cells are present in the glands, sometimes in large numbers. These changes occur more or less uniformly throughout the gland, no normal glandular structure being found even in the smallest of the affected glands. The difference in the consistence of various glands depends upon whether the overgrowth has occurred chiefly in the reticulum or in the endothelial cells. When the former is in excess the glands are hard and fibrotic, whereas excess of the "lymphadenoma cells" renders them soft. In some the process of fibrosis continues till the gland becomes hard and firm in consistence. Finally only a mass of fibrous tissue may represent the adenoid tissue of the gland (G. Sharp).

Spleen.—In a large majority of the cases the spleen is diseased. In 100 cases in which the condition of the spleen was noted, it was found affected in 78; in the other 22 no change was described. This organ is thus more or less changed in four-fifths of the cases. The enlargement, as a rule, is only slight or moderate in degree; in a few rare cases it has reached a large size. The weight, however, is seldom more than thirty ounces. In one of my cases, in a boy aged thirteen, it weighed 23½ ounces. The enlargement may be a simple hypertrophy, or it may be

due to the presence of lymphadenoid growths of various sizes in the substance of the spleen. In 78 cases in which the spleen was affected, these growths were found in 57; in the remaining 21 it was only described as being enlarged. When there is simple increase in size of the spleen it is generally firm in consistence: it may be hard, but it is rarely soft. The Malpighian corpuscles are often easily seen, being rather larger than in a normal spleen. When the lymphoid growths which originate in the Malpighian bodies are present, they do not, as a rule, cause any great enlargement of the spleen. They vary in size and may be no larger than peas, or as big as crab-apples. The appearance of the growths is peculiar, and they have been compared to masses of suet or cold fat. In one case, on which I made the post-mortem examination, the cut surface of the spleen which contained these growths resembled a piece of brawn in appearance. The masses are often irregular in shape, and may even bulge out the capsule of the overlying spleen. Infarctions also are often seen in the spleen; their appearance varies with their age. Chronic inflammation of the capsule of the spleen is not uncommon, and leads to the formation of adhesions to surrounding organs and thickening of the capsule.

Microscopically the trabeculae of the spleen are thickened from increase in the amount of their fibrous elements. The lymphoid growths which are developed in the Malpighian corpuscles resemble the enlarged lymphatic glands in structure. As in them there is a reticulum, in the meshes of which lie small round cells. New fibrous tissue is developed in which the connective-tissue corpuscles are seen; the amount of fibrous tissue may increase till the Malpighian bodies consist almost entirely of it. In this stage the lymphoid cells are few in number. Round the edges of the Malpighian bodies may be seen masses of brown pigment; this pigment is derived from degenerated and broken-up red blood-corpuscles which were included in the growth of the fibrous tissue. When the nodules of new growth are large, they compress the surrounding splenic pulp; it is then frequently atrophied, and contains cells which have undergone fatty degeneration and granules of pigment. In some cases there is hyperplasia of the splenic pulp. Lardaceous change in the spleen has rarely been observed.

The medulla of bones is sometimes altered, but in other cases it is normal. By microscopical examination it has been determined that the altered condition of the marrow is due to a growth of lymphadenoma in the place of the normal bone-marrow.

Alimentary Canal.—Along the whole length of the normal alimentary canal are scattered numerous patches of adenoid tissue. In almost any of these centres a development of lymphadenoid tissue may take place in Hodgkin's disease; and, once started, it may extend considerably beyond the original patch. The follicles at the back of the tongue may be enlarged, and the adenoid tissue of which the tonsils principally consist may become considerably increased in amount, leading to enlargement of the tonsils, sometimes followed by ulceration.

Adenoid growths have been found in the mucous membrane of the pharynx and of the oesophagus. In the stomach there may be extensive overgrowth of the adenoid tissue and general thickening of the mucous membrane in consequence. Ulceration of this thickened mucous membrane may occur at several different points. In the intestines the special aggregations of adenoid tissue, which occur in the solitary glands and in the Peyer's patches, may become considerably enlarged from overgrowth of adenoid tissue. This change is most marked in the lower part of the ileum, but it may extend beyond the ileo-caecal valve into the ascending colon. The adenoid growth may extend considerably in the mucous coat of the intestine without invading the muscular coat. Dr. Pitt describes one form which is confined to the mucous and submucous coats, especially in the ileo-caecal region, and another which occupies the subserous lymphatics, and by invading the muscular coats leads to dilatation of the intestine. Dr. R. N. Salaman, however, considers that many intestinal growths described as lymphadenoma are really lymphosarcoma (*vide Vol. III. p. 577.*)

Liver.—In a considerable number of cases changes are found in the liver which may or may not be sufficient to cause an actual increase in the size of the organ. Most frequently lymphoid growths are found scattered throughout the liver; these are generally small, varying in size from a pin's head to a cherry-stone, and white in colour; in some cases the growths may reach the size of a cherry, but these are fewer in number. In appearance they resemble the nodules already described in the spleen. Microscopically the minute growths consist, as elsewhere, of lymphadenoid tissue. Dr. H. D. Rolleston describes the growth as commencing in the portal spaces, and extending between and into the lobules where it develops between the liver-cells, and causes atrophy of the latter by pressure. Burdon-Sanderson considered that the growth may sometimes originate in the tissue of the acinus itself. In some cases there is a general diffuse growth of nucleated tissue in the interlobular spaces, from which extensions may also take place into the tissue of the acini. Occasionally the enlargement of the liver is partly due to congestion of the capillaries. Ascites is not uncommon as a result of portal obstruction by lymphadenoid growths; in some cases the peritoneum is studded with small growths.

Pancreas, see p. 305.

Respiratory System.—In the lungs, growths of adenoid tissue are found which may occur either as the result of direct extension of growth from bronchial glands already affected into the lung itself, or as separate centres of growth scattered throughout both lungs. The scattered growths which generally originate in the peribronchial lymphatic tissue are small in size, and resemble tubercles in appearance. They have the same structure as the growths in other organs, and seldom soften or break down. Effusions into the pleural cavity are found in some cases, and may contain blood. Lymphadenomatous growths are rarely found beneath the pleura.

Heart.—The heart is often small, and fatty change in the muscular

wall is not uncommon. Occasionally adenoid growths have been found in the substance of the heart or on its surface.

Genito-urinary System.—Lymphadenoid growths similar in structure to those found in other abdominal viscera occur also in the kidney. These are usually small, and rarely grow larger than a cherry. The growths generally develop between the tubules in the cortex of the kidney, and as they enlarge they may, by pressure, cause atrophy of the epithelium lining the tubules. The kidney may be enlarged as a whole; it is, as a rule, pale in colour, and sometimes it is the seat of fatty or lardaceous change. The testicles, like other glands, may contain growths, which lead to atrophy of the epithelium by compression. The ovaries are rarely affected.

Ductless Glands.—The thymus may be enlarged, or it may contain adenoid growths, which may extend to the surrounding parts. Most frequently the anterior mediastinal glands are primarily affected, and the thymus by extension of the growths from them.

The suprarenals were affected in one case recorded by Sir W. Gowers. The thyroid gland may also be involved (Stengel).

Nervous System.—Lymphadenomatous growths occasionally occur in the dura mater, but rarely in the brain or elsewhere in the nervous system.

Skin.—In rare cases adenoid growths have been found in the skin.

Pathogeny.—From consideration of the many points of analogy between lymphadenoma and tuberculosis, and the other infective processes, it seems very probable that it is also due to infection. The clinical features of the disease, and especially its acute course, the haemorrhages, the anaemia, and in some cases the presence of fever tend to support this probability. The changes which we find in the adenoid tissues and lymphatic glands are most easily explained by assuming that they are the result of the action of some pathogenetic parasite. Evidence of direct infection in lymphadenoma is almost entirely wanting; but one case, which was under the care of Obratzow, is of importance in this respect. An assistant, who helped to plug the nose and also to examine the urine and faeces of a patient with acute Hodgkin's disease, was soon afterwards attacked by the same disease, and died a month after the time of the alleged infection. Another point in favour of the infective nature of lymphadenoma is the occurrence of the same disease in the lower animals: the lymphadenoma of cattle, dogs, and horses appears to be identical with that of man. In this respect, again, it resembles tuberculosis. In horses especially the disease presents many of the same symptoms as in man, for in equine lymphadenoma there is enlargement of the lymphatic glands, and in some cases adenoid growths in the spleen, liver, kidneys, and lungs. Emaciation, anaemia, and leukaemia may also occur. In 1907 Longcope failed to produce lymphadenoma in monkeys by injections of emulsions of fresh lymphadenomatous glands. If the disease be due to infection we have as yet no knowledge of the organism which is the immediate cause of it. We do not even

know whether it is an animal or vegetable parasite. As Dreschfeld pointed out, there is a close analogy between the varieties of chronic and acute Hodgkin's disease and the various forms of tuberculosis. Though Dreschfeld found small bacilli in the kidney of one case, these were not present in specimens examined from other cases; and he was unable to obtain any growth of micro-organism from pieces of the diseased glands placed in various culture media. The experiments of Delbet suggest that the disease is due to a certain bacillus, but they require further extension and confirmation. This observer found a bacillus in the blood of the spleen of a woman who was suffering from lymphadenoma (*lymphadénome généralisé*), in which the spleen was also affected. He obtained pure cultivations of this micro-organism, with which he made experimental inoculations in a dog. Large doses of a pure culture of the bacillus were employed, and the inoculations were repeated several times at various intervals. This method of experiment was adopted by Delbet, as he considered the bacillus to be one of feeble virulence, and unable to multiply in the tissues of a healthy animal unless reinforced by repeated doses of the culture. The animal emaciated rapidly, and in fifteen days it lost more than one-fifth of its weight. When the dog was killed, a month after the commencement of the inoculations, the lymphatic glands in the mesentery and in the mesocolon, the thoracic and vertebral glands, as well as those in both axillæ and in the right groin, were found enlarged. On examining the enlarged glands Delbet was able to shew that they contained the same bacillus which he had inoculated as a pure culture. On the strength of this experiment he claims to have produced a generalised lymphadenoma by inoculations of this bacillus. Other observers have found micrococci, and no bacilli, in the enlarged glands. Blood-cultures in Libman's hands were negative. White and Proescher describe *Spirochaeta lymphatica* in lymphadenoma, acute lymphæmia, and lymphosarcoma, and speak of all these diseases as lymphatic spirilloses. Thus it is evident that the whole matter requires far more extensive experimental investigation before any satisfactory explanation of the pathology of this disease can be given.

Varieties.—Different forms of lymphadenoma occur which may be classified in various ways according to their clinical manifestations. The chief points in which cases differ from one another are the distribution of the glandular enlargements, the consistence of the enlarged glands, the condition of the spleen and other viscera, the state of the blood, and the course of the disease. Thus, in some cases one group of glands only is enlarged; in others, several groups; in others, again, almost all the lymphatic glands. When the disease is general the enlargement may be uniform, or some glands may be much more increased in size than others. In some cases the glands are soft, in others hard; but no sharp distinction can be made between the two, as both hard and soft glands may occur together in the same patient, and the glands may be hard at one stage of the disease and soft at another. It has been thought that when the glands are soft the blood contains an excess of leucocytes, but this

distinction does not hold good ; for in some cases with soft glands there is no leucocytosis, whilst on the other hand it may exist when the glands are hard. In any of the varieties I have mentioned there may or may not be enlargement of the spleen or changes in the other organs due to the presence of lymphadenoid growths. The course of the disease varies considerably, and it is convenient to speak of an acute and a chronic form of Hodgkin's disease. Dreschfeld described three forms of the acute disease : one in which the superficial glands were enlarged, a second in which the intrathoracic, and the third in which the intra-abdominal glands and abdominal organs were affected.

Symptoms.—General.—The most important symptoms in lymphadenoma are enlargement of the lymphatic glands, anaemia, enlargement of the spleen, rise of temperature, progressive loss of strength, and emaciation. Some other less frequent symptoms will also be considered presently. Enlargement of the superficial lymphatic glands is the most frequent of the early symptoms, as in more than half of the cases it is the first change to attract the attention of the patient. When the glands, which are deeply situated, are enlarged early, the symptoms caused by their pressure upon the surrounding organs may occur before any other sign of the disease. Thus, pain in the chest and cough, pain in the abdomen, pain or oedema of the legs, according as the thoracic or abdominal glands are first affected, may be the earliest symptoms. In other cases the general constitutional symptoms, such as anaemia, loss of weight and weakness, are the first indications of loss of health ; and the glandular enlargement may not become apparent until later. Rarely an irregular form of fever may precede the glandular enlargement.

Lymphatic Glands.—**Early enlargement.**—The superficial lymphatic glands are usually enlarged before the deeper glands ; thus, Sir W. Gowers found in 52 out of 78 cases that enlargement of these glands was the first detected symptom of the disease. Of the superficial groups of glands the cervical are more often enlarged at the beginning of the disease than any other group. The enlargement may be limited at first to one side of the neck. In some cases many months, or even three years, as in a case recorded by Prof. Osler, may elapse before those on the opposite side become affected. Less frequently the inguinal glands, and rarely those in the axilla, are the first to become affected.

Characters of Enlargement.—The lymphatic glands increase in size at first independently of each other, and remain separate. This condition may continue until they are as large as pigeon's eggs. The skin is freely movable over the superficial glands, as neither it nor the surrounding tissues are invaded unless some secondary infection takes place ; and in the early stages of the disease the different members of a group of glands can be moved one upon another. Later the glands often become firmly adherent to each other, as the result of periadenitis, or of the extension of growth from one gland to another. In this manner large lobulated masses or tumours are formed which may attain the size of a cocoa-nut. The consistence of the enlarged glands depends chiefly upon the rate of

growth. If the enlargement take place slowly, they remain firm to the touch ; if the increase in size be rapid, they are soft. As a rule the enlarged glands do not cause any pain, nor are they tender when pressed. Occasionally some pain may be felt in the glands if they are undergoing rapid enlargement, and a mass of enlarged glands may cause direct or referred pain by pressing upon a nerve or nerve-trunk. The progress of the enlargement varies considerably in different cases, and also in different groups of glands in the same patient. Thus, enlargement may take place more rapidly at one time than another, or one set of glands may increase considerably in size while others remain nearly stationary. In some cases the glands get larger and larger until death takes place. In others the growth becomes arrested, and in a small number the size of the glands diminishes before death occurs. In the neck the enlargement generally begins in the glands of the posterior triangle, or in those which lie beneath the lower jaw. The suboccipital glands are often enlarged also. Frequently the submaxillary glands are enlarged on both sides. The natural contour of the neck is then much distorted by the masses of enlarged glands, which may reach a large size and greatly increase its circumference. When the enlargement of the cervical glands is considerable, serious secondary symptoms may be produced by the pressure which they exert upon important structures in the neck. The larynx may be displaced laterally, or the trachea may be so much narrowed by pressure that great dyspnoea and even death may occur. Difficulty in swallowing and death from starvation may be caused by compression of the oesophagus. Pressure on the blood-vessels may lead to anaemia of the brain if the carotid arteries be concerned, or to venous congestion if the veins are affected. The vagus nerve is sometimes compressed, and this may lead to irregularity of the pulse and cardiac failure. The glandular growth may extend into the pharynx, so that swallowing becomes difficult and hearing imperfect. Extensive enlargement of the submaxillary glands impedes the movements of the lower jaw. If the enlargement of the axillary glands be considerable, movement of the arm is difficult. Pain and swelling may be caused by pressure upon the nerves and veins in the axilla. In the groin the enlarged glands may compress the femoral vein so as to produce oedema of the leg, or even thrombosis in the vein itself. The thoracic veins may be enlarged, and all the symptoms of an intrathoracic tumour may be present ; the most frequent being spasmodic cough and dyspnoea. The organs in the chest, such as the bronchi, may be compressed by the glands. The superior vena cava may be narrowed or even occluded, leading to oedema of the head and arms ; a collateral circulation may then be established by the mammary and epigastric veins, as in a case recorded by Prof. Osler. The left azygos vein may be compressed and hydrothorax occur in consequence. In one such case I aspirated a left-sided pleural effusion on several occasions at intervals of about a fortnight, during which it re-accumulated. When the glands in the abdomen are much enlarged they can be felt through the abdominal wall. They may

press upon the inferior vena cava, or the common iliac veins, and may thus cause oedema of the legs. The solar plexus may be implicated, with bronzing of the skin, though the suprarenals are unaffected. Cases have been observed by Sir W. Gowers, Dr. Fowler, Guay, Féreol, and Prof. Osler. Vomiting may be excited by pressure upon the stomach, or sciatic pain by pressure upon the sacral plexus. The enlarged glands may compress the ureters, or they may become adherent to the uterus and simulate a uterine myoma.

The Spleen.—The spleen is frequently enlarged, but the enlargement is not an early symptom, and as a rule it cannot be detected until the glandular enlargement has become well marked. The spleen never reaches the enormous size which is so frequently seen in cases of myelaemia, though it is generally large enough for the lower end of it to be felt beneath the costal margin. It sometimes extends as far as the middle line, but it rarely causes any pain or discomfort. Occasionally it is irregular in outline owing to the large nodules of adenoid growth.

Circulatory System.—*Blood.*—Anaemia is common. It frequently appears very early; but in some cases it may not appear until after the glands have become enlarged. It is of the secondary type, and may be profound. The consequences of the anaemia are weariness, lack of energy, oedema of the feet or even of the subcutaneous tissues generally. Haemorrhages may occur from the mucous membranes, and specially from the nose, in the subcutaneous tissue, or in the retina. When the blood is drawn it looks pale, but clear, if there be no excess of leucocytes. If there be an excess of leucocytes it looks rather milky. Coagulation takes place slowly and imperfectly.

Red blood-corpuses.—The microscopic appearances of the blood vary in different cases, and the anaemia is much more marked in some cases than it is in others. In many there are 50 or 60 per cent of the normal number of red blood-corpuses, but in a few severe cases they are as few as 25 per cent. In seven cases observed by Reed the number of red corpuscles varied between 2,670,000 and 5,264,000 per c.mm., and the amount of haemoglobin between 51 per cent and 84 per cent. Changes in the red corpuscles sometimes occur both in the acute and in the chronic form of Hodgkin's disease. Small red corpuscles or microcytes may occur in varying numbers; in some cases they are numerous. Irregular forms of red corpuscles which are generally included under the name of poikilocytes may also be observed. Nucleated red corpuscles are rarely seen. Dreschfeld did not find any in his cases.

Leucocytes.—In the majority of cases there is no leucocytosis. Thus, Sir W. Gowers found that out of 64 cases there was no leucocytosis in 39; in 25 there was some excess of white corpuscles. In Reed's cases the number of leucocytes varied between 6200 and 15,500 per c.mm., and the ratio between white and red corpuscles from 1:210 to 1:624. If there be leucocytosis, and the leucocytes may be increased up to 25,000 per c.mm., it is chiefly due to the presence of an increased number of the polymorphonuclears. In the absence of leucocytosis,

however, a differential count may shew increase of the mononuclears at the expense of the polymorphonuclears. Ehrlich considered that the presence of an increased number of eosinophil leucocytes in the blood is an important characteristic of the blood in lymphadenoma and in leukaemia. Out of 20 cases Pepper found eosinophilia varying from 8·8 to 16 per cent. in 4. Dreschfeld found the eosinophils fairly numerous in some cases, but scanty in others; and concluded, in opposition to Ehrlich, that they are not of much value as an aid to diagnosis. Kanthack considered that the eosinophil cells are of no diagnostic value either in Hodgkin's disease or in leukaemia, because they have been found in large numbers in gonorrhœal pus, in many specimens of pus both from man and from the lower animals, in sputum, and in muco-purulent nasal secretions.

Heart.—The action of the heart may be weak if there be fatty degeneration from anaemia. In fever the frequency of the pulse is of course increased, and it may be irregular if the vagus nerve is compressed by enlarged glands in the neck.

Alimentary System.—In the mouth the gums may be soft, pale in colour, and swollen, and blood may be extravasated beneath the mucous membrane. As already mentioned, the tonsils may be considerably enlarged, and there may be extensive adenoid growths in the pharynx. The presence of lymphoid growths in the wall of the stomach leads to dyspepsia and vomiting; when there is ulceration of the growths the symptoms resemble those of simple gastric ulcer; vomiting may also be excited by the pressure of enlarged lymphatic glands upon the stomach itself. Lymphadenoma of the intestine may cause no inconvenience, or it may be accompanied by diarrhoea and haemorrhage. Constipation may be caused by the pressure of enlarged abdominal glands upon the bowel. As a rule there are no symptoms of hepatic disorder. Obstructive jaundice sometimes occurs from the pressure of enlarged glands upon the common bile-duct, as in a case recently under my care in the Newcastle Infirmary. The liver is uniformly enlarged, owing, in some cases, to the excessive development of lymphoid growths in the substance of the organ. The association of considerable enlargement and a hectic temperature has imitated hepatic abscess so closely as to lead to a fruitless operation.

Respiratory System.—Dyspnoea is a frequent symptom; it may arise either from narrowing of the trachea by the pressure of enlarged glands, or from the anaemia. Bronchitis is often present. The lymphoid growths may give rise to crepitations which are audible in different parts of the chest, but do not otherwise interfere with respiration. Effusion into the pleural cavity may occur, either as part of a general anasarca or as a result of pressure upon the azygos or bronchial veins.

Nervous System.—In some cases delirium and coma have occurred. One of Mosler's patients died from oedema of the brain. Various symptoms may be produced by the pressure of the enlarged glands upon the nerves. Thus, pressure upon the cervical sympathetic may cause inequality in the size of the pupils. Pains in the nerves of the arms

and legs may also be the result of pressure. Prof. Osler has observed one case of paraplegia from pressure upon the spinal cord.

Genito-urinary System.—As a rule there are no renal symptoms even when lymphoid growths are found in the kidney after death. The urine may contain traces of albumin; but anything more than this may be taken as evidence of ulterior changes in the kidney occurring as a complication. Amenorrhoea is common, and is probably a result of the anaemia. In some cases pregnancy has occurred after the onset of the disease.

Temperature.—The temperature in cases of Hodgkin's disease has been very carefully studied by Sir W. Gowers, who found that fever was present as a symptom of the disease itself in two-thirds of the cases in which the temperature had been taken. It is rather more frequent in acute than in chronic cases, and it occurs in nearly all patients under twenty years of age. When general swelling of the glands occurs at the beginning of the disease, fever is often an early symptom. Sir W. Gowers describes three modes in which pyrexia may occur. In the first the temperature is continuously raised from two to five degrees above the normal, and only varies a degree or a degree and a half during the twenty-four hours. In the second mode there are periods, several days in duration, of high fever alternating with periods of normal temperature. In a third there are marked daily variations, the temperature rising to 101° or 103° F. each evening, and falling to 100° or even to normal in the morning. Dr. F. Taylor has shewn that a fourth or relapsing form of fever occurs in a few cases. When present, this mode of pyrexia may be an important aid in distinguishing this malady from other chronic infections in which the three former forms of fever are common whilst the relapsing form is very rare. Dr. Taylor gives a good example of this mode of pyrexia in a case shewing five periods of pyrexia which varied from seven to thirty days in duration with four intervals, of relative or absolute apyrexia, varying from six to seventeen days in length. At the commencement of each febrile period the temperature may rise gradually during four or five days to 102° , as in a case recorded by Pel, remain high for a period extending sometimes to fifteen days, and then fall again by a lysis occupying three or four days. The course of the fever thus differs from that of true relapsing fever in which there is a rapid rise to 106° or 107° followed by a crisis in which the temperature falls to normal in the course of twelve or fifteen hours. The temperature, which is raised in the majority of cases of lymphadenoma, may therefore be either continuous, remittent, intermittent, or relapsing.

Skin.—Owing to the anaemia the skin and mucous membranes are pale, often from the onset of the symptoms. Sometimes there is a general subcutaneous oedema. Bronzing of the skin, as in Addison's disease, has been observed in a few cases (*vide* p. 471). Profuse perspiration occurs during the night in some cases. In rare instances pruritus is troublesome.

Ordinary Course, Duration, and Termination.—The onset of the disease varies considerably in different cases. In some there is at first a localised swelling of one group of glands only, and this condition may persist even for several years without further extension. A primary local disease may be followed at a variable interval by a general enlargement of the glands, or there may be a general enlargement of most of the lymphatic glands at the outset. Generalisation of the disease is accompanied, or soon followed, by progressive anaemia; the anaemia may appear, however, before the glands are appreciably affected. In acute cases the onset may be marked by shivering, pains in the back and limbs, cough and expectoration, and rapid loss of strength.

In acute cases the patient rapidly becomes worse. In chronic cases the disease may remain stationary for considerable periods. The duration of the disease varies from five or six weeks, in very acute cases, to several years in the chronic forms of the disease. Sir W. Gowers gives the following table, drawn up from forty-nine fatal cases, in which the duration of the disease had been ascertained:—

Less than 1 year in 18 cases.					
Between 1 and 2 years in 15 cases.					
"	2	"	3	"	6 "
"	3	"	4	"	6 "
"	4	"	5	"	3 "
Over 5 years 1 case.					

Most of the cases, therefore, live less than four years.

Sex appears to have little or no influence upon the duration of the disease. Before middle life the duration does not vary at different ages; it is shorter, however, in the second than in the first half of life.

Recovery may take place under treatment. This is more likely to occur in chronic than in acute cases, though marked improvement or arrest may occur even in the latter.

Sooner or later, in most cases, the anaemia becomes more intense, the patient loses strength, and dies from exhaustion. In some cases the immediate cause of death has been asphyxia from the pressure of enlarged glands upon the trachea or bronchi. Death has also taken place from starvation owing to pressure upon the oesophagus. In a few cases coma and convulsions have occurred at the end. Loss of blood and diarrhoea may also take part in bringing about a fatal termination. Death may also be the result of some complication, such as pneumonia, oedema of the lungs, or pleural effusion, whilst a considerable number ultimately die from tuberculosis.

Diagnosis.—The enlargement of the lymphatic glands which takes place in lymphadenoma must be distinguished from other kinds of enlargement. In advanced cases the number of glands affected and the general cachexia render the diagnosis easy. In the early stages of

the disease, when only a few glands may be affected and the severe constitutional symptoms not fully manifested, the enlargement has to be distinguished from those of acute adenitis, tuberculous lymphadenitis, sarcoma, and carcinoma. The disease, as a whole, has also to be distinguished from myelaemic and lymphocytic leukaemia. In very acute cases the symptoms may resemble those of the known infections, especially when the abdominal glands are principally affected ; in these cases we may have to distinguish between acute lymphadenoma and typhoid fever, relapsing fever, tuberculous peritonitis, or septicaemia ; or again, the symptoms of Hodgkin's disease may suggest purpura or pernicious anaemia. In some of these febrile cases, and especially when internal glands only are enlarged which cannot be clearly discerned during life, careful attention to the course of the fever may aid the diagnosis. When the pyrexia is of the relapsing type and a fourth or fifth relapse occurs of equal severity and duration with the first and terminating by lysis and not by crisis, and the *Spirochaeta obermeieri* is not found in the blood, true relapsing fever may be excluded, and the presence of lymphadenoma strongly suspected.

Acute Adenitis.—In acute inflammation of the lymphatic glands the enlargement takes place rapidly, and the glands are painful and tender. The surrounding tissues are also frequently inflamed at the same time. A few glands only are affected, and, as a rule, they are directly connected with some part in which inflammation, suppuration, or a breach of surface open to microbes is already known. In lymphadenoma the enlargement is painless ; it is unaccompanied by inflammation, and it frequently affects a large number of glands, not necessarily in contiguity.

Tuberculous disease of the lymphatic glands is generally limited to one or more groups. It frequently begins in glands which, like the cervical glands, are connected with some surface through which the tubercle bacillus may enter. Thus, if the enlargement of the lymphatic glands be general, it is almost certainly not tuberculous. Again, in the several groups of glands we find that in tuberculous disease there is often periadenitis, which leads to matting of the glands ; whereas, in lymphadenoma, as the surrounding tissues are not inflamed, the glands remain freely movable. In tuberculous disease the glands soon begin to caseate or suppurate, the skin is implicated, it gives way, and the abscess discharges through the opening ; in lymphadenoma the glands neither caseate nor suppurate, nor is the skin inflamed about them. Lymphadenomatous glands, as a rule, reach a larger size than tuberculous glands, probably because degenerative changes generally occur early in the latter. Not infrequently, however, when the enlargement is confined to a few glands a diagnosis cannot be made until some further manifestation of the true nature of the enlargement appears. Thus, in a case under my care the enlargement of the cervical glands on both sides was of four years' duration, and appeared to be due to lymphadenoma until a slight haemoptysis followed by the appearance of tubercle bacilli in the sputum determined the true nature of the disease. In such cases

help may be obtained from the tuberculin reaction, and possibly from estimating the opsonic index.

Sarcoma.—In the early stages of lymphadenoma, when the glandular enlargement is confined to a small area, there may be difficulty in distinguishing it from sarcoma of the glands. In sarcoma, however, there is extension of the growth to neighbouring glands and into the surrounding tissues, whereas in lymphadenoma further extensions will probably arise in a different part of the body. So generalised an enlargement would not be sarcoma. In sarcoma, again, the presence of secondary or primary growth elsewhere may help to clear up the diagnosis. By some writers the name lymphosarcoma has been used as a synonym for lymphadenoma; by others this name has been given to a special form of sarcoma of the lymphatic glands. This confusion should be guarded against.

Secondary carcinoma of the lymphatic glands is not likely to be confounded with that due to lymphadenoma, as the presence of the primary growth indicates the true character of the glandular swelling also.

In some cases, when the nature of the enlargement of the lymphatic glands is doubtful, the administration of arsenic may aid the diagnosis. Any marked diminution in the size of the glands under the influence of the drug would indicate Hodgkin's disease rather than sarcoma or carcinoma.

Leukaemia, strictly speaking, is only a symptom and not a disease. As a symptom we have seen that it occurs in some cases of lymphadenoma. Myelaemia or myelogenous leukaemia is distinguished from lymphadenoma by the absence of any early enlargement of the lymphatic glands, by the great enlargement of the spleen, and by the presence in the blood of myelocytes. Prof. Muir has found that in this form of leukaemia they may form more than 50 per cent of the white corpuscles present in the blood. In some cases of myelogenous leukaemia an enlargement of the lymphatic glands takes place as a late event. The enlargement is then secondary to that of the spleen and to the leukaemia, and thus differs from the primary granular enlargement of Hodgkin's disease.

In lymphocytic leukaemia the glands are, as a rule, not so firm in consistence as in lymphadenoma. The main distinction is, however, made by examination of the blood. In lymphadenoma, when there is an excess of leucocytes, and there may be as many as 25,000 per c.mm., it is almost entirely due to increase in the polymorphonuclear leucocytes, whereas in lymphocytic leukaemia the excess is due to the presence of lymphocytes. Prof. Muir (*vide Vol. V. p. 661, 1898*), however, points out that in children with enlarged glands the diagnosis may be difficult on account of a certain excess of lymphocytes in the blood, and that several examinations of the blood may be necessary before a correct conclusion can be drawn.

Syphilis.—Enlargement of the lymphatic glands, most directly connected with the primary seat of infection, is a constant primary symptom

of syphilis. In the male the usual primary enlargement of the glands in the groin is not likely to be mistaken for lymphadenoma, as in all such cases a careful inspection of the genital organs would naturally be the first step in the examination of the case, and the discovery of a sore with an indurated base would at once explain the condition of the lymphatic glands. In the female and in cases of primary syphilitic infection of other parts of the body, the true cause of the enlargement might be overlooked, so that it is important in any doubtful case to remember the chief characteristics of this form of enlargement. In considering the possibility of syphilis as a cause of any glandular swelling, careful inquiry and search must be made for the presence of the original indurated sore, which appears about twenty-four days after infection has taken place, and is followed by the enlargement of the nearest lymphatic glands in seven to fourteen days. One gland is usually enlarged first, the other members of the same group becoming affected soon afterwards. The glands are hard in consistence, and seldom exceed a marble in size. The inguinal glands on each side are by far the most commonly affected groups, but the axillary and cervical glands are enlarged in cases of primary infection of the upper limb or face. The enlargement rarely extends beyond the nearest group of glands, and even if untreated tends in time to subside. In lymphadenoma the glands soon reach a larger size, and are softer in consistence, and the disease tends to spread to other groups of glands. Some enlargement of the lymphatic glands may occur in the later stages of syphilis, but its nature would be explained by the presence of some secondary or tertiary manifestations in the neighbourhood of the enlarged glands.

Prognosis.—In cases of acute Hodgkin's disease the prognosis is very unfavourable; the patient rapidly loses strength and dies of exhaustion. Pulmonary complications frequently occur in these cases, so that pneumonia, pleurisy, or phthisis may be the actual cause of death. But acute cases are not always fatal. Dreschfeld has recorded that in one acute case with cough, fever, intense anaemia, rapid enlargement of the lymphatic glands causing obstruction of the right bronchus, enlargement of the spleen, leucocytosis and rapid loss of weight, the lymphatic glands decreased, under treatment by arsenic, nearly to their normal size: the spleen fell to its usual size, the temperature became normal, the blood improved, and the patient became convalescent. If the glands be enlarged in several regions, and reach a large size, the prognosis is grave. The actual progress of the disease is not uniform. If the patient's health has been good up to the time of the beginning of the disease, its advances appear to be less rapid than in patients in whom the onset was preceded by some ill-health. Thus, in cases in which the symptoms have first appeared after pregnancy, or after a loss of blood, the downward progress has generally been more rapid than in cases in which the health had previously been good. A marked decrease in the number of red corpuscles in the blood, and a distinct increase

in the number of the white, severally indicate that the case is a serious one. So long as the enlarged glands remain soft there is a better prospect of recovery. Hardness of the glands indicates fibrosis. Fever, especially if it be continuous, is an indication that the disease is acute. Oedema is a grave symptom ; it generally indicates that death is not far distant.

Treatment.—In the treatment of lymphadenoma we have two main objects in view. In the first place, we must endeavour to combat the disease by treatment of the structures which have already become affected, so as to prevent its spreading to other parts of the body ; in the second place, we have to increase the resisting power of the patient as far as possible. We have seen that in some cases the disease is local at first, tending to become general at a later stage. In this respect it resembles tuberculous disease of the lymphatic glands, in which we have abundant evidence that early local treatment is frequently successful both in curing the local disease and in averting general tuberculosis. As it is probable that lymphadenoma is likewise due to the presence of some infective agent, the strictly localised forms of the disease in superficial glands appear to be suitable for surgical treatment. The special indications for removal of the glands will be considered on p. 479.

General Hygienic Treatment.—It is important that those who suffer from lymphadenoma should lead quiet, regular lives and avoid all bodily fatigue. The diet should be light, nourishing, and easily digested. It is doubtful whether climate has much influence upon the course of the malady, but bathing in mineral waters, as at Kreuznach or Woodhall Spa, has seemed beneficial in some cases.

Local Treatment.—In certain cases of lymphadenoma there can be no doubt that removal of the diseased glands is the right method of treatment to adopt. The clinical course of some cases appears to indicate clearly that the disease in the first instance is local, and confined to a few lymphatic glands ; moreover, that the further spread of the disease takes place from the part first affected, by a process which we may provisionally call secondary infection. In such cases the early removal of the enlarged glands may arrest the disease. One of our chief difficulties is to select the cases most suitable for such treatment. If the disease be general from the first, or if it has spread to deep lymphatic glands which cannot be removed, radical surgical treatment is no longer possible. By some physicians, however, removal of as many of the diseased glands as possible has been recommended even in cases in which several distinct groups are affected ; not so much with the object of eradicating the disease, as of diminishing the number of the diseased glands in the hope that medicinal treatment may thereby be better able to deal with the remnant. In such cases, however, operative treatment has proved unsatisfactory, and when several groups of glands are affected, it is very doubtful whether partial removal is advisable. Evidence is still wanting to shew that medicinal treatment is rendered more efficient by removal of some only of the enlarged glands.

Operative treatment to give relief from urgent symptoms due to pressure will be considered presently. The most suitable cases for radical operation are those in which the enlargement is confined to one group of glands, in which the spleen is not enlarged, and in which there is neither fever nor well-marked anaemia. The presence of a few enlarged glands in other situations, or a slight enlargement of the spleen, need not preclude operation if other conditions seem favourable; but the results are not likely to be so good. It is important to take the temperature night and morning for a few days before deciding upon an operation, that the absence of fever may be definitely ascertained. Sir W. Gowers considers that when the number of the red corpuscles is below 60 per cent, removal of the glands should not be attempted. A marked leucocytosis is also unfavourable to operation. The success which may attend the removal of the diseased glands in suitable cases is well illustrated by three cases, mentioned by Sir W. Gowers, in which the operation was performed by Verneuil. In one case a large glandular tumour, which compressed the trachea, was removed from the neck; seven years afterwards the patient remained in good health. In another case the glands in the axilla had been enlarged for two years, and had reached the size of a child's head when they were removed. Subsequently another enlarged gland was removed from the neck, and one or two glands afterwards became enlarged and suppurated. The operative treatment was supplemented by the administration of arsenic, and the patient remained free from the disease up to the time of his death, from acute pneumonia, six years after the first operation. In a third case the removal of the enlarged glands stayed the progress of the disease for some years, though it finally became generalised and ended fatally. In certain circumstances an operation becomes necessary to relieve urgent symptoms. Thus, if the trachea, or an important nerve or blood-vessel, be compressed by an enlarged gland which can be removed, this should be done; although the operation may not be likely to check the general progress of the disease. The difficulty of the operation for removal of the glands varies very much. In some cases the enlarged glands are easily separated from the surrounding structures; in others the deeper parts of the glandular mass may be adherent and the removal by no means easy.

Many other means of local treatment have been advocated and carried out in practice. None of them, however, has proved so effectual as extirpation; so that, when possible, removal is the most efficient method. Various solutions have been injected into the substance of the glands. Thus, among other drugs, arsenic, iodine, potassium iodide, silver nitrate, carbolic acid, and chromic acid have been employed. Such injections are often painful, and may lead to inflammation and suppuration of the diseased glands; very little benefit has been obtained by such methods, and the inflammation excited may prove troublesome. Galvanopuncture has likewise proved to be of little service in reducing the size of the glands. Various simple methods of local treatment have also

been employed, such as massage, alternate hot and cold douching, and the application of ice. Such means of treatment are less harmful, but they lead to little diminution in the size of the glands. The application of blisters to the skin, over the enlarged glands, has in some cases been followed by a reduction in size. The application of iodine to the skin over the enlarged glands is of little or no use.

One of the most valuable methods of treatment is by α -rays. The α -rays should be applied for fifteen minutes about twice a week, or as often as possible without injury to the skin overlying the enlarged glands. Superficial glands undergo a rapid diminution in size in many cases, or the further enlargement of a rapidly growing gland may be checked by this method of treatment.

Medicinal Treatment.—Of all the drugs which have been used in the treatment of lymphadenoma, arsenic has most frequently proved to be of service. I have seen marked improvement follow the administration of arsenic, and cases have been recorded in which the glandular swellings have disappeared, and the patient has recovered under its influence. Not only may arsenic do good in chronic cases, but even in acute cases very good results may follow its use. Arsenic may most conveniently be given in solution; the dose being increased gradually. It is a good plan to begin with five minims of liquor arsenicalis three times a day, and this dose may by degrees be increased up to fifteen or twenty minims three times a day, provided that the patient exhibits no toxic symptoms. It should be given in milk with or just after food. If symptoms of intolerance arise, the arsenic should be discontinued for a few days. In some cases the Fowler's solution has been injected directly into the enlarged glands, but the injections may cause pain, and even inflammation and suppuration; and the results have not been so good as when given by the mouth. Reclus has recorded one case in which the cervical glands on each side of the neck were affected; arsenical solution was both given by the mouth and injected into the glands, and these diminished in size until only some small nodules remained. In two other cases this treatment proved successful, but in three others the result was unfavourable. Valuable as arsenic proves in the treatment of some cases of Hodgkin's disease, there are others in which little or no benefit appears to result from its use. The mode of action of arsenic in this disease is not known. It may have a germicidal action, comparable with that of mercury in syphilis and of quinine in ague, or it may be an antidote to some chemical poison.

Iodine has been frequently used both as tincture of iodine and as potassium iodide. There is, however, but little evidence to shew that it has had any useful influence upon the progress of the disease. In some cases the depressing effect of potassium iodide may be distinctly harmful. Phosphorus has been used with good effects in a few cases, but it is certainly less useful than arsenic. One patient under the observation of Sir Clifford Allbutt recovered from a grave and apparently extreme attack of the disease while taking tungstate of sodium, but the drug proved

useless in all cases subsequently under his care. Mercurial inunction was found beneficial in one case by Dreschfield, but it must be used with caution so as to avoid any symptoms of mercurialism. Iron, cod-liver oil, and quinine have been used as general tonics. Organic extracts prepared from various glandular and other tissues have of late been extensively used in the treatment of disease; but in the present state of our knowledge of the pathology of lymphadenoma, it is difficult to conceive that any organic extract can be of special service in the treatment of this malady. We have seen that the lymphatic glands, spleen, thymus gland, and bone-marrow are all liable to be affected in certain cases of Hodgkin's disease. For this reason both spleen and lymphatic gland and thymus extract, as well as bone-marrow, have been employed, but with no very decisive result.

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STATUS LYMPHATICUS

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SYNONYMS.—*Lymphatism*; *Status Thymicus*.

Definition.—The status lymphaticus is a condition of bodily debility which is characterised by hyperplasia of the thymus and of the lymphoid tissues generally throughout the body; and also, especially in adult cases, by hypoplasia of the heart and of the arterial system. It is accompanied by a great lowering of the patient's power of resistance, and is believed to account for a large number of otherwise unexplained cases of sudden death.

Historical.—It is a very old and often-repeated observation that enlargement of the thymus is often the chief discoverable lesion in cases of sudden death from apparently insufficient causes. With regard to this coincidence there can be no doubt, but its explanation is very obscure and has given rise to great difference of opinion.

Kopp and various others among the older writers believed that the hypertrophied thymus caused death by setting up a fatal laryngismus—which they designated “thymic asthma.” That ordinary laryngismus is due to thymic enlargement is a view which is no longer held, although it is certain that many children with hyperplasia of the thymus have glottic spasm. Probably, as Escherich has suggested, the laryngismus in these cases is only a symptom of a general nervous irritability and has nothing directly to do with the large thymus. The mechanical pressure of the hypertrophied thymus on the trachea or bronchi, or even on the lungs, has been thought by many distinguished pathologists and clinicians to play an important part in the causation of “thymus death.” This view has been supported by many authorities, such as Virchow, Cohnheim, Jacobi, Rauchfuss, Somma, Grawitz, Beneke, and Pott: and, although it is difficult to believe that it is often the main cause of death in these cases, it cannot be denied that it is probably sometimes an auxiliary factor. To some it has seemed that the fatal syncope may be induced either by direct pressure of the enlarged organ on the heart, or by the heart becoming engorged owing to pressure on the large vessels (vena cava, innominate vein, pulmonary artery, or aorta). Others have thought it more probable that it is the nerves (either vagus, recurrent laryngeal, phrenic, or sympathetic) that are pressed on. None of these hypotheses, however, has been at all generally accepted by those who have investigated the subject.

In 1889 Arnold Paltauf formulated a new hypothesis which has met with much more general approval. In his opinion it was not proved that “thymus death” was ever due to pressure of the enlarged thymus

on the trachea, blood-vessels, or nerves ; and he attributed it to the patient's having a peculiar "lymphatico-chlorotic" constitution which he called the Status Lymphaticus. This dyscrasia he described as being characterised by a general enlargement of all the lymphoid tissues of the body, the enlarged thymus being merely one of its manifestations. The constitutional weakness was, in his opinion, sufficient to account for the fatal syncope as well as for all the other symptoms. Although Paltauf's description of the status lymphaticus may not have gained acceptance in all its particulars, and is still regarded with doubt in some quarters—especially among medico-legal writers—it has been cordially received by many leading pathologists and physicians. Until further light on the question is forthcoming, it may therefore be held to rank as a recognised clinical entity ; and it is treated as such in this article.

Etiology.—The cause of the status lymphaticus is quite unknown. It has been pointed out that in early childhood most of the patients are rickety ; but they are certainly not all so. The condition is occasionally found in several members of a family.

Morbid Anatomy.—In all cases of status lymphaticus the *thymus* is above the normal size, and often the enlargement is very great. According to Bovaird and Nicoll the normal thymus weighs about $1\frac{1}{2}$ drams (6 grms.) at the time of birth and does not ordinarily grow any larger in after-life. In lymphatism it may weigh from $2\frac{1}{2}$ drams to $1\frac{1}{2}$ oz. (10 to 50 grms.) or more. Its texture shews little change on naked-eye examination, but under the microscope, according to Blumer, there is "a general hyperplasia of the lymphoid elements associated at times with proliferation of the endothelial cells lying along the trabeculae of the organ."

The *lymphoid structures* throughout the body are enlarged. This is most noticeable in those situated internally, such as the bronchial and mesenteric lymphatic glands and the Peyer's patches and solitary glands of the bowel. The tonsils and the other lymphoid tissues in the pharynx and naso-pharynx, and at the root of the tongue, are also hypertrophied ; and the lymphatic glands all over the body are more or less enlarged. The *spleen* is large owing to an increase in the size of the Malpighian bodies ; and occasionally enlargement of the *thyroid* has been present. In the *bones* the place of the normal yellow marrow is found to have been largely taken by red. The microscopical changes in the various lymphoid tissues are similar to those in the thymus, already described. They closely resemble the lesions in various infective conditions (Blumer).

Hypoplasia of the *vascular system*, like that in chlorosis, has been described by Paltauf and others, especially in older children and adults. In these also there is apt to be a degree of infantilism.

Pathology.—Why such a lymphatic habit of body should give rise to such a dangerous state of weakness of the heart and nervous system is still unexplained, but various suggestions have been made. Escherich has proposed that there is a sort of hyperthyrmisation of the blood which sets up a constant state of latent irritable weakness in the nervous

system so that trivial causes have unexpectedly severe effects. He would thus regard lymphatism as due to disordered function of the thymus in the same way that myxoedema and exophthalmic goitre depend on disordered thyroid action. Švehla endeavoured to prove this by experiment. He found that the intravenous injection of thymus extract from various animals caused, in dogs, a lowering of the blood-pressure from vasomotor paralysis along with quickening of the pulse from direct action on the heart. When large doses were given, the animal died with symptoms very similar to those of thymus death—namely, restlessness, followed by collapse and dyspnoea. It has, however, been pointed out by Swale Vincent that this proves very little, because extracts of nervous, glandular, muscular, and other tissues all produce a fall of the blood-pressure when injected into animals in this way. According to Blumer there is no reason to believe that the thymus possesses an internal secretion, and he suggests that the abnormal condition is more probably one of intermittent lympho-toxaemia.

Clinical Features.—These are usually rather indefinite. The patient is pale, flabby, and rather fat. If, as often happens, he is a baby he is apt to be rickety and may be subject to laryngismus. The tonsils and the adenoid tissues in the naso-pharynx are hypertrophied and the spleen is palpable. The superficially situated lymphatic glands shew some degree of enlargement; and occasionally the hypertrophy of the thymus may be made out by percussion. A degree of lymphocytosis has sometimes been found (Ewing).

Very often the presence of these somewhat vague signs of lymphatism is overlooked, the child is thought to be quite well, and if sudden death occurs it is altogether unexpected. When serious symptoms set in, they sometimes take the form of ill-defined convulsive seizures accompanied by faintness, cyanosis, and dyspnoea; and these may go on recurring at intervals for many weeks or months before the end comes. In most instances, however, no such alarming symptoms occur to give a hint of danger until the fatal syncope sets in after some slight exertion or shock, or without any such occasion being apparent. The child then becomes rapidly faint, gasping and cyanosed, his eyes turn up and he loses consciousness. There may, or may not, be convulsive movements. The heart stops altogether before the respirations cease. The apparent exciting cause of the fatal seizure may be of the most trifling kind—the use of a tongue-depressor (Pott), a wet pack (Escherich), or a hypodermic injection. The sudden death of Prof. Langerhans's boy, after a prophylactic injection of antidiphtheritic serum, was the means of calling attention to this subject very forcibly some years ago. In some cases death follows a sudden plunge into water, and, in these, the usual signs of death from drowning are absent (Paltauf, Nordmann). In others it occurs during chloroform or other anaesthesia. Sometimes, also, it takes place during convalescence from infectious diseases, such as diphtheria or enteric fever (Escherich, Daut, Friedjung).

It is always, apparently, the result of syncope and not of laryngeal obstruction. Tracheotomy and artificial respiration are therefore of no use whatever.

Diagnosis.—The symptoms by which the presence of lymphatism can be recognised during life are so ill-defined and uncharacteristic that its diagnosis must, probably, always be more or less a matter of conjecture.

Prognosis.—There is no reason to believe that the status lymphaticus always ends fatally. At the same time, when its presence is suspected, a very guarded prognosis must always be given because of the feeble hold on life which such a condition implies.

Treatment.—No form of treatment can be said to have any beneficial effect on the lymphatic dyscrasia. Suspicion of its presence should, however, make us exceedingly careful about administering an anaesthetic, or even a wet pack, that is not necessary, or doing any operation, however trivial, that is not urgently called for. When sudden syncope occurs no known treatment is of any avail.

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J. T.

INFANTILISM

By JOHN THOMSON, M.D., F.R.C.P. Ed.

Introductory.—The first detailed description of infantilism appears to have been given by Lorain in 1871 in the preface to the thesis of his pupil, Faneau de la Cour. Long before this, however, the condition had been recognised as worthy of study by Andral, Tardieu, Lasègue, and others. The interest now taken in the subject is largely due to French writers (Brissaud, Hertoghe, Meige, and Apert). As the various authors who have made use of the word have not always applied it with quite the same meaning, it may be well, in the first place, to define what it really signifies. The essential change indicating that an individual has passed from childhood and become an adult consists, not in the increased size and strength, but in the advent of maturity of the genital organs. Along with this acquisition of the "primary sexual characteristics" of adult life, the so-called "secondary sexual characteristics" of body and mind gradually appear. The lineaments become more marked and prominent; the figure loses its childish contour and shews the characteristic male or female peculiarities; the larynx enlarges and the voice changes; the breasts, in the female, enlarge; there is an increased growth of the sebaceous glands, and hair appears in the pubic and axillary regions, and, in the male, on the face. At the same time, the epiphyses of the long bones all over the body gradually become united to the shafts, and the power of further growth ultimately ceases. These bodily changes are accompanied by corresponding alterations in the individual's emotional and intellectual nature. Failure of the primary and secondary sexual characteristics to appear at the proper time constitutes infantilism, and this is equally so whether the general body-growth be diminutive, normal, or gigantic. Properly speaking, therefore, infantilism merely denotes a group of symptoms—just as paralysis, idiocy, or dyspepsia do—and not a disease. So long, however, as our knowledge of the intimate pathology of the subject remains in its present rudimentary condition, it is advisable, as well as convenient, to use the word somewhat loosely in this respect.

Etiology.—In many cases of infantilism the underlying abnormal condition obviously dates from birth or early infancy. In other

instances the arrest of growth and other associated symptoms begin more or less suddenly during later childhood. Lastly, in a few recorded cases, infantilism sets in in adult life; for example, in two men who had already shewn signs of virility (Gandy), and in a woman who had not only menstruated normally but had even borne a child (Brissaud and Bauer). The course of the characteristic symptoms also varies in different cases; in many, after having once appeared, they remain unchanged; in some, adult characteristics, though greatly delayed, gradually make their appearance without any special treatment. In a few, the onset of the belated puberty is rapid and complete without any apparent cause, and, in many of those cases in which special organs are affected, normal development takes place promptly on the administration of the appropriate remedy.

So little is at present known of many of the conditions which cause infantilism that no satisfactory classification of the cases is possible as yet. Most of the forms which have been described, however, may be arranged under one or other of the three following headings, though it must be admitted that indefinite cases are sometimes met with which are very hard to classify:—(1) *Idiopathic* cases, in which no serious general or local disease is discoverable. (2) *Cachectic* cases, in which serious general disease or poisoning exists. (3) Cases more or less certainly due to *gross lesions or defects of some important internal organ*.

I. *Idiopathic Infantilism*.—This may be held to include the class of cases generally alluded to as of the "Lorain type." It has been called anangioplastic infantilism, in accordance with the hypothesis that the backward growth depends on a defective development of the vascular system in general, and it has also been ranked by some authorities as a form of developmental defect or stigma of degeneration (Féré). Some of the cases generally assigned to this group are regarded by Mr. Hastings Gilford as instances of the condition he described as ateleiosis. In the Lorain type, when adult age is reached, the figure is very small and slim, and, on this account, looks at first sight like that of a young child. When the patient is stripped, however, his outlines are seen to be not altogether child-like although his size is so. The head is proportionally small and the trunk well formed—with the shoulders broader than the hips and the bony prominences fairly distinct. Although the patient's size is that of a young boy or girl, the contour is that of one approaching puberty. There is, however, no sign of pubic, axillary, or facial hair, and, in the female, no development of the breasts; the genital organs are small and immature. The intelligence may be fairly normal, but it is generally rather small, weak, and childish like the body.

II. *Cachectic infantilism* may conveniently be applied to those cases in which the arrest of development seems to depend on some chronic infective or other disease, or on some drug-intoxication which profoundly affects the general constitution. The type of this variety of infantilism is often less marked and less characteristic than that of the other two. The cachexia first, and probably still most frequently, referred to in

medical literature as causing infantilism is chronic *tuberculosis*. The children of tuberculous parents are said to be prone to suffer from infantilism of the Lorain type. But what concerns us now is that children who have long suffered from severe tuberculosis in any part are apt to shew signs of retarded sexual development. Spinal caries is a very common causal factor (Marie and Léri, Andrieu). *Congenital syphilis* is another common cause (Ed. Fournier). Many of the children who suffer severely from hereditary syphilis in early infancy shew in adolescence greatly delayed sexual development. *Malaria* (Lancereaux), *leprosy*, *pellagra*, and, to a less extent, some of the common infective diseases have also been credited with a similar effect. Infantilism is not rarely associated with *heart disease* of various kinds (Ferrannini, Carré, Jesson); apparently any form of heart disease that begins early in life and causes much interference with the general circulation may give rise to it. The lesions most often described as causing it are mitral stenosis and congenital stenosis of the pulmonary and aortic orifices. In only a few of the diseases which give rise to idiocy (besides cretinism) is infantilism a prominent feature. It is especially so in cases of severe *spastic diplegia* and of *microcephaly*. It is not one of the features of mongolism. In dwarfing from severe *rickets* there is generally considerable delay in sexual development. In many other forms of dwarfing, such as achondroplasia and the well-known type of which "General Tom Thumb" and Count Boruwlaski were examples, infantilism does not occur.

The *drugs* which, when used for a long time and in excessive doses, are regarded as most apt to cause infantilism, are alcohol, lead, mercury, morphine, tobacco, and bisulphide of carbon.

III. Infantilism depending on gross lesions or defects of important internal organs.—This group includes much the most important and interesting types of the condition. Hertoghe, who is a great authority on all clinical matters relating to the thyroid and has especially studied its action on the body-growth, is strongly of opinion that all forms of infantilism depend on defective thyroid action only, and that without thyroid defect infantilism cannot occur. Other writers, such as Brissaud, hold similar views. There are, however, as Ferrannini has pointed out, many cogent reasons for doubting this altogether. Indeed, it seems almost certain that whilst the thyroid has a far more striking effect than any other gland on the development of the sexual organs and on that of the body generally, many other important internal organs exert a similar influence in a very definite degree. Some reported cases, indeed, seem to suggest, if not to prove, that extensive lesions of almost any one of the important viscera may sometimes produce infantilism.

Thyroid or myxoedematous infantilism, called by some French writers "Brissaud's type," in contradistinction to "Lorain's," is synonymous with Hertoghe's *myxoédème fruste* or benign chronic hypothyria in the child. It is, indeed, the mildest degree of cretinism, and its symptoms are so slight that its nature is often overlooked. The features of a characteristic case are well seen in Fig. 8, and may be described as follows

(Meige) :—The face is rounded, the cheeks chubby, the eyes slightly puffy, the lips thick, the nose more or less snubbed ; but the skin is soft and delicate, the hair fine, and the eyebrows and eyelashes rather scanty. The abdomen is somewhat large, the limbs are plump but tapering towards their extremities, and all the bony and muscular prominences of the body are masked by a thick layer of fat. The genital organs are rudimentary ; the penis is small, and the testes, though well formed and completely descended, are those of a little boy. There is no pubic or axillary hair. The voice is harsh and cracked, the larynx very slightly prominent, and the thyroid gland generally small. The head is rather large for the size of the body, just as in children ; and, although the stature is not invariably small, the whole conformation of the figure is childish—the lower limbs,



FIG. 8.—Case of Myxoedematous Infantilism (Hertoghe), shewing effect of thyroid treatment during five years (1895-1900). In 1895 the patient was twenty years old and 46 inches in height. In 1900 he had gained 11½ inches. (Reproduced by Dr. Hertoghe's kind permission from the *Bull. Acad. roy. de méd. de Brux.*, Séance du 27 avril 1907.)

for example, being too short and the abdomen too large for the patient's age. When the symptoms set in early, the second dentition may be delayed indefinitely (Marfan and Guinon), and, as Hertoghe first pointed out, the epiphyses remain ununited, so that there is a possibility of later growth in stature. Along with the arrest of bodily growth there is often a characteristic defect of some of the functions. Constipation is often present, sometimes enuresis ; there may be a tendency to very heavy sleep ; habitual cold feet and chilblains are common, and the temperature is generally subnormal. The mental condition also is, as a rule, characteristically childish ; the patient is heedless and simple-minded, laughs or cries easily, is quick-tempered but readily appeased, prone to excessive fondness and to unreasoning dislikes. When myxoedematous infantilism occurs in females, its effect on the figure and on development is similar to that seen in the male sex. The infantile

woman remains a big girl, and the age of puberty does not bring about the usual changes. Menstruation is in abeyance, the breasts do not enlarge, the neck shews no thyroid prominence, and no hair appears on the axillae or pubes. As the hips enlarge very little, the trunk remains of a cylindrical shape, and there is no waist.

Infantilism associated with *gigantism* is not uncommon, and a number of adult giants have been described in whom the proportions of the body were boyish, the union of the epiphyses and diaphyses delayed, and the genital organs like those of a child. Gigantism, according to Brissaud and others, is to be regarded as the acromegaly of adolescence, and in almost all the cases examined after death disease of the pituitary body has been found (Launois and Roy). It seems, therefore, possible, and perhaps probable, that the morbid condition of the pituitary gland present may have something to do with the arrest of sexual development. There is, however, no case as yet on record in which the administration of pituitary gland substance has started the delayed sexual development.

Dr. Eustace Smith and others have drawn attention to the marked arrest of growth which is sometimes observed in children who, year after year, are afflicted with recurrent attacks of *severe diarrhoea*. When such children reach adult age they often shew a condition of complete infantilism, their height, bodily proportions, sexual organs, and mental state being those of children of 9 or 10 years, and their epiphyses still ununited to the diaphyses. In many such cases the original diarrhoea is certainly due to severe pancreatic disease. In 1904 Dr. Byrom Bramwell published the case of a boy of $18\frac{1}{2}$ years, with marked infantilism which had not benefited by thyroid. He proved, by the use of Sahli's iodoform capsules and other tests, that the pancreatic secretion was completely in abeyance in this patient, and shewed that when pancreatic substance was regularly administered the arrested growth and development resumed their normal course. In $2\frac{1}{2}$ years the boy gained 5*g* in. in height and $23\frac{1}{2}$ lbs. in weight; his genital organs developed normally, as did many of the accessory sexual characteristics; pubic and axillary hair appeared, he lost his childish voice and, to a considerable extent, the childish proportions of his figure; and his diarrhoea ceased. As a similarly successful case has been recorded by Dr. J. L. Rentoul, there seems to be no doubt that Dr. Byrom Bramwell has established that there is a distinct clinical entity—a *pancreatic form* of infantilism—which is due to deficient pancreatic secretion. With the gratifying success of these cases in mind, it is very disappointing to have to record that all cases of infantilism with pancreatic disease cannot be cured in this way. In a case precisely similar to those just mentioned, a boy of $24\frac{1}{2}$ years (31) whose clinical history and appearance (Fig. 9) were almost identical with those of Dr. Bramwell's patient, and who also had been treated in vain with thyroid, the pancreatic treatment was ordered by Dr. Bramwell and myself without success. The patient shewed no improvement worth noting after more than a year. It is also certain that in some patients presenting a similar appearance and having

a similar history of recurrent diarrhoea the pancreas seems to be functionally active (4). The causation of these cases remains quite obscure.

Infantilism has also been described as occurring in cases of *hypertrophic biliary hepatic cirrhosis* (Lereboullet); and Morlat has published a case in which *suprarenal inadequacy* was possibly the cause of infantilism.

Treatment.—In all cases of infantilism it is important to attend



FIG. 9.—Case of Pancreatic Infantilism; 24½ years old. Height 51½ inches. Severe recurrent pancreatic diarrhoea for 11½ years; ossification like that of a boy of 7 to 9 years of age; no improvement on thyroid or on pancreatic extract.

carefully, in the first place, to the general health and hygiene, and to treat any cause of cachexia that may be present. In thyroid infantilism the treatment is, of course, that of myxoedema. Thyroid substance should not, however, be given in too large amount; one 5-grain tablet every second day is generally a sufficient dose to begin with. The result is always striking; but if thyroid treatment is not begun before the age of adolescence the lower extremities will always remain stunted (Fig. 8).

In the pancreatic form pancreatic extract should be given in some form. Dr. Bramwell gave his patient 1 dram of Armour's Liquor pan-

creaticus daily along with an equal amount of a glycerin extract of steapsin. Dr. Rentoul's case received 10 grains of pancreatic extract thrice a day.

In all forms of infantilism it is advisable to give small doses of thyroid a careful trial. Occasionally it may be unexpectedly successful; and, with care, it will in any case do no harm.

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OBESITY

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Introduction.—Obesity may be defined as a condition in which, from one cause or another, an overgrowth of fat takes place in many parts of the body. The body in health is more or less covered with fatty tissue, and certain parts are well clad, both without and within. Improved nutrition of the whole body increases the fat, and diminished nutrition is rapidly indicated by a loss of it. We are only concerned now to take note of such adipose overgrowth as constitutes an unwholesome or morbid state, leading to undue bulk, disproportionate body-weight, and interference

with due performance of various functions. "Le développement de la grasse ne constitue une maladie que lorsqu'elle entrave le jeu d'un organe quelconque" (P. Legendre).

Etiology.—In this case we have to deal with a definite tissue-proneness, which, as in other instances, may be either inherited or acquired. A family tendency to obesity is well recognised; but the several members of such a family may not all become the subjects of it. Mode of life has much to do in determining the occurrence of obesity, and thus singular unlikeness may exist amongst the individuals of a disposed stock. Such a tendency may be noted in certain members of a family inheriting the arthritic diathesis; gout or glycosuria, for example, occurring in some members, and an extraordinary obesity in others.

The sexual relations of pinguescence are noteworthy, and must be considered in taking a complete view of the subject. Adipose development is as normal a mode of nutrition at puberty in the woman as is the development of the breasts and ovaries. In this connexion we note also the increased tendency to fatty deposition which is apt to ensue after castration, especially in females. Towards the age of forty years the same tendency is to be noted in both sexes—the change in such cases being partly due to diminished bodily activity and the easier life not seldom enjoyed at this period.

Undue obesity is, as a rule, no indication of soundness or robustness of constitution. In infancy an excess of fat is not a sign of general good nutrition. Thus, a child may be at once very rickety and very fat; and the latter state is apt to deceive the unwary as to the serious underlying condition. In hysterical girls there may be noteworthy obesity in spite of a miserable appetite and a very small intake of food. The breasts may become very fat in women the subjects of amenorrhoea; and the condition subsides on re-establishment of the menses. Atrophy of the testicles has been known to be associated with inordinate growth of mammary fat in males. The sexual appetite is distinctly lowered in obese persons; and inertness of the sexual organs certainly favours the deposit of fat. As pointed out by Sir James Paget, after the age of forty years persons either diverge into spareness or become more or less obese; the former, as a rule, enjoy the happier and longer lease of life (*vide Vol. I. p. 203*). With advancing years, however, a good deal of the adventitious obesity of middle life is apt to be absorbed and disappear.

Heredity apart, the conditions which determine obesity in a morbid degree are diet, exercise, and habits of life. In cases presenting a strong hereditary tendency to fatty hypertrophy, habits of diet count for less, and the proclivity may be little influenced by measures which prove effective in other cases.

We are not now concerned to discuss cases of local overgrowths of fat or fatty tumours. These may be single or multiple, of slow or of rapid growth. Such tumours are commonly hereditary, as much so as are atheromatous cysts or wens. Habits have little, if anything to do with

these. Two exceptions may, however, be mentioned : first, cases in which local irritation, long continued, induces a fatty growth ; and, secondly, cases of symmetrical fatty tumours (lipoma), over the occipital region, due to excessive beer-drinking, described by the late Mr. Morrant Baker : of these I have seen a good many examples (*vide p. 507*).

We may also note some racial peculiarities in respect of obesity. The peculiar gluteal development of the Hottentot women deserves mention ; and the common tendency to obesity in the Hebrew race is remarkable. A singular contrast is to be observed between the Teutonic races and the people of the United States of America. The former often present examples of obesity ; the latter, although largely recruited from the former, exhibit markedly less tendency to this condition amidst the environments of the New World. Climate may have to do with this result ; but habits and diet are probably much more concerned in it. In the East remarkable examples of obesity are met with, but amongst Hindus rather than Mohammedans. Customs and diet account for this difference ; and European indulgences, including alcoholic habits, united with Oriental indolence, not seldom explain these anomalies.

In a moderately fat man the fat has been estimated at one-eighteenth or one-twentieth of the total body-weight ; and in woman the relative proportion is larger. It is naturally found in the face, in the orbits, palms of the hands, soles of the feet, flexures of joints, around the kidneys (suet), in the mesentery and omentum, in the appendices epiploicae, in the subcutaneous areolar tissue in certain situations, such as the abdominal wall, mammary region, and in the cancellous tissue of bones, especially in yellow marrow. No fat is met with in the scrotum or penis, or in the nymphæ ; nor is there any between the rectum and bladder. None is found within the cranium. In the viscera fat is normally met with in the cells of the liver.

The sources of fat in the system are dependent on the supply of food. One of the common signs of excessive consumption of food is a progressive obesity. Fatty matters reach the blood from both animal and vegetable pabulum, but especially from non-nitrogenised materials, such as starch, sugar, gum, and alcohol. Fat itself affords an immediate supply ; but only a small proportion of the stored fat in the body comes directly from that consumed with the food. "Fat and carbohydrate are on an equal footing as sources of muscular energy" (Chittenden). Excessive pinguescence is normally kept in check by the means which induce full oxygenation of the blood and tissues. Hence, if organic compounds rich in carbon are fully supplied, and oxygen but inadequately, favouring conditions exist for fatty deposition. Diminished exercise and close confinement lessen oxygenation by preventing the dissipation of carbon compounds. These points are well illustrated by the results of captivity on animals, and by examples only too common in the social systems of the human family ; and they afford a clue at once to the nature of the proper remedial measures. The only pathological condition in which it may be affirmed that the relative consumption of oxygen and the

excretion of carbonic acid are decidedly reduced, is that of obesity. This explains the difficulty met with in reducing the weight of some patients even when subjected to an appropriate diet. It is generally thought that in some obese persons the condition is independent of over-eating or deficient exercise, and is due to retarded metabolism; after considerable discussion von Noorden comes to the conclusion that this interpretation must be accepted with reserve.

As pathologists and clinical observers we have to distinguish, as far as we can, between fattiness due to infiltration and that due to degeneration. In the former case infiltration (lipomatosis) should be regarded as an excessive deposition in the cells which normally contain fat, as in the subcutaneous areolar tissue, omentum, perinephric region, liver, and parts between muscular fasciculi in the voluntary and cardiac muscles. Such an infiltration, though general, may in certain parts be in excess; it is then met with, especially in the abdomen and in the integuments about the mammary region and the buttocks. In the heart, infiltration is common, and is not inconsistent with vigorous action of this organ. The visceral layer of the pericardium is a common seat of it; so also is the interstitial connective tissue. This is not to be regarded as an example of "fatty heart," since the muscular (sarcous) elements may be quite healthy in such a case. Obese persons may have abundant fatty accumulation amongst their muscular bundles, and such muscles, though hampered and weak, may be sufficiently sound to resume full function if they be relieved of their fatty encumbrance. Obesity tends to induce inaction and muscular inability, and so there is a vicious circle of malign events in such instances. The liver becomes fatty under similar conditions, as where persons eat fatty food or much carbohydrate material; and especially if they are immoderate in alcoholic fluids, which combine more readily with oxygen than does fat. Fatty degeneration is a more serious matter. In this case fat is found in the tissue-elements themselves, as in the muscle fibres or in the walls of blood-vessels (*vide Vol. I. p. 573*).

We are only concerned here to consider fatty deposit and infiltration in excess. Fat is apt to be deposited in excess after anaemia due to repeated haemorrhages or otherwise; and is commonly met with in chlorotic young women. In wasting disease fat is lost early; and in cases of inanition it is observed to disappear early from the face, giving rise to a characteristic starved and gaunt aspect. Fat is often fluctuating in quantity; much of it may disappear in a very short time, and no less rapidly may it be again deposited. Human and animal fat contains olein or liquid fat, and stearin or palmitin which are solid. The sources of it, as already stated, are from various articles of diet, and an ordinary dietary contains from one to two and a half ounces of fat. Carbohydrates, such as starch and sugar, especially tend to produce it; but the method of conversion of sugar into fat is not yet precisely ascertained. It is probable that fat can be also converted into carbohydrates, such as dextrose, its carbon being thus transformed for use in the tissues as a soluble and readily diffusible carbohydrate. This may conceivably

occur when the body has to draw upon its own store of fat and so lose its undue corpulence.

That the proteins possibly constitute a source of fat is proved by the fact that whilst the urea which is excreted represents all the nitrogen which is thus passed through the body, it represents much less carbon than is found in a quantity of the protein yielding the same amount of nitrogen. This surplus of carbon, if not otherwise disposed of, for example as CO_2 , remains as a possible source of fat to be deposited in the body. The chemical problem of the formation of fat out of protein is contained in the question of the production of sugar out of protein, and of the building up of fat out of sugar (Magnus-Levy).

Normal blood contains about one-half per cent of fat, the muscles more than 3 per cent, the brain 8 per cent, and the nerves 22 per cent. The nerves are the last to lose their fat in cases of general atrophy, and the large amount normally present in them is significant of the high importance of fat to their well-being and potential activity. The amount of fat in the blood may be readily increased by certain articles of food—mostly by fat, sugar, and starchy matters; in less degree by animal food, and least of all by bread.

Fat is a bad conductor of heat. Warmth is retained in the body by the panniculus adiposus, and the intestines are especially protected by the fat in the omentum and appendices epiploicae. Hence the stout require less warm clothing than lean persons; and the latter suffer more readily from chills and exposure. Normal radiation of heat is checked in the obese; there are, however, exceptions to the tolerance of cold in some cases of anaemic obesity.

It is not sufficiently recognised that fat deposits are constantly undergoing change by decomposition and reformation. As with all other tissues, intimate change proceeds even in the densest layers of fat; and in no part of the body does any fatty deposit lie out of the current of life and unaltered.

I have said that heredity has largely to do with the occurrence of obesity; according to Oertel of Munich this influence can be traced in 50 per cent of all cases. We have, then, to deal with a very definite diathetic condition in which a special trophic process is at work—one as definite in its course and outcome as in that in which a gouty or a “strumous” disposition prevails. It is of high importance to realise this, and, if possible, to come to some clear understanding of it before undertaking a line of treatment for any obese person; for a marked difference is to be noted between cases in which obesity is the outcome of heredity and those in which the encumbrance is acquired by certain habits and modes of life. Where hereditary disposition is potent and effective we are less hopeful by far of good and lasting results from any plan of treatment. When the disorder is acquired by bad habits, improper diet, and indolence, we may readily modify it; and, in patients who co-operate intelligently and honestly, we may largely and permanently dissipate the fatty encumbrance. The mental peculiarities and temperament are deeply concerned

in every case ; the difficulties of treatment are greatly enhanced in persons of indolent and phlegmatic habit ; and proportionately diminished in persons of active and energetic disposition.

The relation between gout and obesity is one of much interest. Gout figures largely in many cases. It is not unusual for certain members of a family with gouty inheritance to become obese. This may occur in either sex and sometimes before puberty. After the age of thirty obesity may set in, and within ten or fifteen years glycosuria. Such persons belong to the class of fat or gouty diabetics, and in them the glycosuria is but a mild form of chronic diabetes. The presence of glucose in the urine is almost the only symptom which such patients have in common with those who are the subjects of the graver disorder. They often have no thirst and but little polyuria, and for many years they lose very little weight. These are the patients who gain much benefit from recourse to spas, and the disorder may sometimes be arrested, or become intermittent. Carefully regulated dietary may occasionally remove all glucose from the urine, or a small percentage of it may persist. If neglected, such cases may drift into incurable forms of diabetes. Pulmonary tuberculosis, furunculosis, or gangrene of the extremities usually terminates life. Diabetic coma is not a very frequent mode of death in these cases. Such patients may live for fifteen or twenty years, or even longer ; and occasionally present acute or chronic phases of gout in some of the joints, with temporary alleviation or removal of the glycosuric state. Such cases are peculiar, and especially striking when met with in families in which other members may be either spare or more overtly gouty ; or exhibit other features of gouty inheritance, such as hemicrania, biliary calculi, or mere lithiasis. Here we may note again the strong hereditary tendency both to obesity and to glycosuria in the Hebrew race. I shall return to the discussion of these cases when considering the appropriate treatment of obesity. A moderate degree of obesity in early life may disappear during adolescence and never recur.

Two leading kinds of obesity are met with in practice, and may be classed as (A) the plethoric, and (B) the anaemic. The former prevails more in men, the latter in women.

A. The Plethoric Kind.—In this kind there is a general over-nutrition, the muscles are large and well developed, and the blood rich in red globules and haemoglobin. The heart hypertrophies and acts at first with vigour, but subsequently it dilates and loses power. The pulse becomes infrequent and of high pressure. Arterial sclerosis is set up, and the vessels become tortuous. As in ordinary cases of heart disease associated with much vascular peripheral resistance, circulatory troubles gradually ensue in the lungs and other organs. Albumin may appear in the urine. Anginal attacks may supervene, and progressive dropsy. Cardiac asthma sometimes occurs, especially at night. The respiration in the later stages may assume the Cheyne-Stokes form. Cerebral hyperaemia, indicated by throbbing of the carotids, vertigo, and tinnitus aurium, is not uncommon : epistaxis may relieve it. Rupture of an

artery in the brain may occur on a sudden increase of intravascular pressure; and in such cases this event is commonly fatal. As cardiac failure progresses arterial pressure falls, and the pulse becomes intermittent or dicrotic.

B. The anaemic kind is characterised mainly by an associated impoverishment of the blood: cases of the plethoric kind may eventually present hydraemic conditions and fall into this category. The obesity may be extreme; but the fatty masses are flabby, and the muscles are ill-developed and feeble. The heart partakes of this muscular inadequacy and acts feebly, the pulse being small. Some elevation of arterial pressure, due to peripheral resistance, may, however, be met with as in ordinary cases of anaemia. In short, we have all the prominent features of anaemia, together with excessive fatty deposition: great incapacity for exertion, ready induction of palpitation and dyspnoea, and small appetite. These patients are neither gross feeders nor always large drinkers. They have often, indeed, an aversion from animal food, and prefer a dietary rich in carbohydrates. The deficiency of haemoglobin in the blood and the consequent inadequate oxygenation maintain and increase the tendency to obesity. As already stated, women are the common subjects of anaemic obesity; and the disorder may be manifested before full growth of the body is established, namely, before the age of twenty-two. Menstruation is generally disordered, or may be absent. Menorrhagia, or losses of blood after child-bearing, may lead subsequently to anaemia and to obesity. This variety is sometimes met with in men after exhausting illnesses, and is not infrequent after enteric fever, rheumatic fever, or pneumonia. It is also witnessed after submission to full mercurial courses for syphilis; but it is not met with in operatives suffering from hydrargyria. Dropsy is common in anaemic obesity. The arterial pressure falls at last, the flow of urine becomes scanty, and, in spite of free perspiration, the tissues become water-logged.

Such patients are altogether more seriously ill than those of the plethoric kind, since the latter may bear with their condition for many years before the blood becomes impoverished and hydraemia sets in. The muscular debility is a factor of supreme importance in the former cases, and adds to the difficulties of successful treatment of the symptoms. Some of these patients present symptoms not unlike those of myxoedema, but do not pass into that condition.

Whether anaemic or plethoric, the subjects of obesity are ill adapted to bear the inroad of acute diseases. Fever, in particular, is very badly borne by them: fatty investment interferes seriously with the dissipation of the heat generated in the body, and thus there is in these cases a special tendency to hyperpyrexia to a degree incompatible with life. Acute fevers and pneumonia are therefore very dangerous maladies for obese persons. Antipyretic measures are seldom effective; and drugs such as quinine, antipyrin, and salicylates are badly borne and may induce collapse. Cold baths in cases fit for it are more successful. If life be saved, convalescence is tardy; and an increase in obesity may occur

in response to the necessary supporting alimentation. This is due to the inherent vicious metabolism which pertains to the trophic habits of such patients.

The line of progressive failure in all these cases may be traced into almost every system of the body. Heart failure and arterial sclerosis have already been referred to. The lungs become the seat of bronchial catarrh, and emphysema may supervene. Gastro-enteric catarrh and gastrectasis from over-eating and drinking may prove troublesome complications. A gouty tendency may lead to lithiasis and to the formation of stone in the kidney. The latter disposition has long been recognised as an appanage of the obese. The liver becomes fatty and greatly enlarged, adding much to the general discomfort and to respiratory incapacity. Gall-stones may form in the gall-bladder and biliary colic occur. The skin becomes unctuous, and comedones and flat greasy warts may be formed. Eczema, erythema, intertrigo, and furuncles are not infrequent; and if alcohol be freely taken, gutta rosacea and hypertrophy of the nose may be present. The causes of death in cases of obesity are syncope, cerebral apoplexy (from degenerate arteries), cardiac rupture, angina pectoris, and uraemia.

Due consideration of the foregoing points should convince any careful practitioner of the futility of treating obese persons by any uniform method. In these cases, as in all cases of disease, regard must be had to the individual and to the personal factors present; and the particular nature of the obesity must be accurately discriminated before any therapeutic measures are attempted. The question of inheritance or of acquirement must be settled, and the patient, and not his symptoms merely, must be treated. Without doubt much harm may be done if a hard and fast line of treatment be indifferently instituted. In this way it is that patients, to reduce their obesity, are sometimes set to pursue dietetic and other measures which may prove not only unavailing but positively mischievous; and others venture to carry out vaunted methods on their own responsibility, not seldom with risks to their general health, which, if unrecognised, are none the less grave.

We must understand, in the first instance, that obesity may be little more than the normal trophic equilibrium for a certain person; and any efforts, seriously pushed, to alter this special conformation may be fraught with risk to his general well-being. As Sir Michael Foster taught: "The same tissue has in different races and different individuals specific and individual characters of nutrition. The flesh of a dog is not the same as that of a man, the muscle of one man lives differently from that of another."

On the other hand, to quote the words of Sir James Paget, "The over-fat are certainly a bad class, especially when the fatness is not hereditary, but may be referred in any degree to their over-eating, soaking, indolence, and defective excretions. The worst of this class are such as have loose, flabby, and yellow fat; and I think you may know them by their bellies being pendulous and more prominent than even

their thick subcutaneous fat accounts for ; for this shape tells of thick omental fat, and I suppose of defective portal circulation. I know no operations in which I more nearly despair of doing good than in those for umbilical hernia or for compound fractures in people that are over-fat after this fashion. Nothing short of the clearest evidence of necessity or of great probable good should lead you to advise cutting operations in people of this kind. Do lithotripsy for them rather than lithotomy ; determine very carefully whether it is absolutely advisable that you should do either ; incline against amputations for even bad compound fractures, and, whenever you can—as, for instance, for cutaneous cysts, haemorrhoids, and the smaller examples of scirrhouss mammary cancers —use caustics rather than the knife or ligature." I venture to believe that with the modern practice of aseptic surgery some of these conditions may now be more safely treated than was possible when Paget wrote.

In any case, it may be strongly urged that the conduct of all such cases should be determined by the clinical skill and carried out under the constant supervision of a well-trained medical man. This much being conceded, it is not too much to affirm, further, that there is nothing special or peculiar in the subject of obesity which any well-educated medical man may not be trusted to deal with. It is necessary to assert this much, because of late years this matter has been absurdly exalted into a "speciality"—a pretension unworthy of our profession and misleading to the general public.

Obesity is recognised by medical officers for life-assurance as an indication of imperfect health. If the body-weight bear an undue proportion to the height of the individual, such cases are either "loaded" or declined as third-class lives. Obese persons bear accidents badly, are unsatisfactory subjects, as we have seen, for surgical operations, and are apt to succumb to serious illnesses. Adults of medium height and fair symmetry, who weigh over fifteen stones, may be considered moderately obese. A weight of twenty stones and over constitutes a grave case ; but examples are on record in which weights of over thirty stones were scaled. Daniel Lambert weighed thirty-two stones at the age of twenty-three, and reached fifty-two stones and eleven pounds in later years.

Occupation and habits of life are familiarly known to induce obesity in certain classes of persons. Sedentary life, whether in or out of doors, favours it. Active members of any profession are not prone to become corpulent unless there be a strongly inherited tendency. Coachmen are apt to suffer unless they groom their horses. Soldiers and sailors do not become obese until they retire from active duties. Sea-captains, owing to their good appetites and limited locomotion, are often victims in spite of their open-air life. In all these cases habits of beer-drinking or of spirit-drinking (even if well diluted) are certain to aggravate the tendency. Cases of extreme obesity may be noted amongst monks, whose duties do not entail much muscular activity; and who, if they eat little meat, often partake largely of fats and carbohydrate matter.

Mental activity, worry, and anxiety all tell against obesity, and so do grief and the irritable or nervous temperament.

Treatment.—*Preventive.*—The main indications are to secure habits of strict temperance in respect of food and drink, and to ensure a life of activity, both mental and bodily. This is especially important when a hereditary tendency to corpulence is present; and it applies to young children and young adults no less than to persons in the third or fourth decades of life. An obese mother is a bad nurse for her infant; a good wet-nurse will be better. If the latter cannot be secured the mother should be dieted, and fatty and carbohydrate foods be restricted as far as possible. Beer should not be taken. Artificial feeding with sterilised cow's-milk is probably better than the maternal milk, and farinaceous food should be excluded, or much reduced in amount, malted food being preferable. In early adult life fat-forming food is to be restricted, and abundant muscular exercise in the open air encouraged. Seaside residence is especially favourable, and sea-bathing when practicable. Later, active exercises are of much value; and athletic pursuits in moderation, such as gymnastics, tennis, riding, rowing, and swimming, may be enjoined with great advantage.

Dietetic.—Without doubt the most remarkable results in diminishing corpulency due to excessive formation and storage of fat in the body are secured by the modification of the ordinary dietary. Modern physiology and chemistry alike indicate the main lines to be followed in this respect. In recent times professional and public attention has been specially devoted to this matter by the successful treatment which was instituted some forty years ago in the case of Mr. Banting by his medical adviser Mr. Harvey. The essential feature of it consisted in the withdrawal of fat-forming food. Mr. Banting took freely of animal food, but ceased to take bread, butter, milk, sugar, potatoes, and sweet wines. No limit was placed on the amount of water, and from six to eight ounces of light red wine were taken daily. On this system forty-six pounds of weight were lost within a year, and although the patient was sixty-six years of age he recovered a large measure of health and comfort. This plan of treatment, while it secures the absence of food that most readily induces obesity, is also characterised by a very large ingestion of nitrogenous matters which are difficult of complete digestion and assimilation. In other cases in which it was employed it provoked indigestion, and caused depression and various nervous symptoms. The quantity of albumin was partly consumed in the production of heat. This method, then, is unsatisfactory in principle and in practice; partly because of the digestive inadequacy of the body to deal with so much nitrogenous matter, and partly because of the slender value of it as a heat-producer within the organism. The nervous system also suffers from deprivation of fatty matters in such a diet. Fatty food is less liable than carbohydrates to cause obesity, being less easily oxidised, and interfering less with the disposal of albuminous matters. In a given weight it contains more potential energy than the carbohydrates.

Experience has plainly shewn that a small proportion both of fat and carbohydrates must be combined with the nitrogenous ingesta in order to ensure normal metabolism; and, to secure a consumption of fat already deposited in the body, muscular exercise must be freely taken to induce increased nitrogenous decomposition. Under these conditions the obese patient loses fat. Muscular activity promotes oxidation of fat, and the small amount consumed in the diet is thus readily disposed of. Carbohydrates are more digestible than fats.

The appetite for food is found to be normal in about half the cases, whilst it is increased in a somewhat smaller number. In some cases the appetite is below the normal.

The influence of fluids, more especially of water, upon fatty deposit is probably considerable when large quantities are consumed. The evil effects of diluted alcohol and saccharine matters are well ascertained. In many cases of obesity there is a marked disposition to drink copiously. Restriction of fluid food will certainly assist greatly in reducing corpulence in such cases as may be treated in this way.

"Bantingism" then, as a system, is both unphysiological and impracticable. Its failure led Ebstein to recommend a modification of it in which fat was permitted, but starchy and saccharine matters almost withheld. Oertel's system of dietary practically corresponds with this; but he enjoins with it graduated exercise, restriction of fluids and fat, and measures to fortify the muscular system generally and the cardiac walls in particular. Schweiniger's system is very similar, but he forbids fluids at meal-times, and prescribes them two hours subsequently. The Salisbury treatment consists in a very free allowance of animal food and entire absence of carbohydrates, large quantities of hot water being taken to wash out the excessive nitrogenous metabolic products from the body (*vide Vol. I. p. 244*). In any case particular attention is to be paid to the condition of the heart, with a view to reinforce it as much as possible. The urine no less demands careful attention; when lithates are abundantly thrown down, the amount of nitrogenous food must be diminished. Deficient excretion of urea demands a similar procedure until a fair percentage is passed, when the diet may be altered in this respect. Bouchard recommends fruit and fresh vegetables containing potash salts, to encourage a freer oxidation of carbohydrates in the diet.

Weir Mitchell and Bouchard recommend a dietary of milk and eggs, and the exclusion of all other food. Thus, for three weeks they prescribe half a pint of milk and an egg every three hours five or six times in the twenty-four hours. At the end of this period they vary the diet in accordance with the general principles just mentioned. The proper ratio between the nitrogenous and carbonaceous elements is fairly maintained by this early treatment. Constipation is likely to occur, and the patient is unfit for much exertion. The monotony of this diet may prove hard to enforce in patients of feeble purpose.

The general principles to be observed in treating cases of obesity relate, then, so far as dietetic measures are concerned, to the restriction

of fats and carbohydrates, and no less to a certain increase in the proteins. The latter augment the metabolism of the whole body. Of food-stuffs a healthy adult requires—of proteins 100 to 130 grms., fats 40 to 80 grms., carbohydrates 450 to 550 grms., salts 30 grms., and water 2800 grms. (*vide Vol. I. p. 216*). The carbohydrates should thus be four or five times in excess of the proteins. Experience shews that all these elements are necessary for perfect nutrition, fatty matters in particular. The fats and carbohydrates, though chemically allied, are subjected to divergent metabolism, and are not mutually interchangeable without risk to the economy. The carbohydrates are believed to supply heat more rapidly than fats—the latter requiring more time to afford this form of energy, having probably first to be converted into sugar.

In treating cases of obesity the patient should be accurately weighed. A careful physical examination of all the organs and secretions of the body should be made, especial attention being paid to the condition of the muscular walls of the heart, the state of the arteries, and the urine. The question as to heredity or acquirement must be noted; the temperament, and the habits of life in respect of food, exercise, and occupation, the age and sex, and the form of the disorder, whether plethoric or anaemic, are to be considered. An inquiry as to gouty proclivity or to haemorrhagic tendency is necessary. The presence of glucose in the urine demands careful attention, and its significance must be gauged as far as possible. Any indication of renal insufficiency, as evinced by a persistently deficient output of urea, is particularly to be noted; because this condition plainly demonstrates the unfitness of the patient to bear a dietary rich in proteins.

Two objects are to be sought in treating any case: *first, to reduce excess of fatty deposits; secondly, to prevent reaccumulation of it.* The first is often more or less easy, but the second is often rendered difficult by restiveness and want of due control on the part of the patient.

The following *dietary* may be usefully enjoined in many cases: Six or eight ounces of hot or cold water may be taken half an hour before breakfast. Breakfast should consist of one or two ounces of well-toasted stale bread with a little butter, grilled white fish, grilled mutton-chop or beefsteak, or cold chicken, game, beef, tongue, or lean ham. One or two small cups of tea or coffee, with a little skimmed milk and without sugar, may be taken. Saccharine may be used as a sweet-flavouring agent, but is commonly disliked. Six ounces of bouillon or clear soup may be taken by weakly patients between breakfast and luncheon, and a gluten or almond biscuit with it. For luncheon order cold meat, or a poached egg with spinach or lettuce, or other green vegetable, as watercress and mustard and cress, or a small omelette. Crust of bread or hard biscuit in small amount is allowable, and a small quantity of fresh butter. A glass of good Bordeaux or Moselle wine (dry) may be taken with as much water. A cup of tea, with a little skimmed milk and a rusk or gluten biscuit, may be taken in the afternoon. For dinner, no soup is to be taken as a rule, but occasionally about eight ounces of a thin

consommé may be allowed ; then a little grilled or boiled fish, without starchy or fatty sauces, but flavoured sometimes with anchovy or some other sauce, oysters, or caviar, a little grilled or roasted meat, mutton, game, or fowl, with a small proportion of fat, green vegetables, no potatoes, and some stewed fruit flavoured with saccharine, or made less tart by the addition of half a teaspoonful of Rochelle salt. Two glasses of claret or of a dry Moselle diluted with water are allowable. Later in the evening a cup of hot weak tea without milk, or as much hot water, should be taken. No malt liquor is permissible.

Such a dietary, adapted for an adult man, is little irksome to any serious patient. It should be continued for some weeks. Women will naturally require smaller quantities of each article. Exercise of any kind is most desirable between meals, and life in the open air is to be carried out as far as possible. Seven hours' sleep is commonly sufficient, and no sleep should be sought except in bed. The patient should lie on a hair mattress and in a well-aired room. Tepid bathing and a cold shower-bath on rising, with good subsequent friction, should be employed daily. Alcohol in the form of diluted brandy or whisky is unadvisable.

Accordingly as weight is lost, the general health being good in all respects, this dietary may be varied with suitable precautions, and a more or less strict attention be paid to the various details of it. Loss of fat should always occur slowly. If the treatment succeed, increased capacity for exercise, brain-work, and a general sense of relief and comfort, perhaps long unfelt and enjoyed, will be experienced. The action of the heart should become more vigorous, the pulse fuller and firmer, the expiration easy, and the urine remain clear on cooling. Tobacco-smoking should be restricted, and used only after meals. The bowels must be relieved daily ; if constipated, moved by two drams of Carlsbad or Homburg salts, or by a dose of "white mixture" while dressing in the morning. If digestion is languid or uncomfortable, a mixture containing dilute nitro-hydrochloric acid and nux vomica, or chiretta, may be taken in the forenoon and afternoon before meals. Cases of anaemic obesity require iron in some form, and the scaly preparations of it are perhaps the most serviceable, given in calumba or quassia infusion.

If fatty accumulation is found to recur with relaxation of the enjoined dietary, either in its quantity or quality, stricter measures will be indicated with a view to maintain as good general health as possible, and also to control the persistent tendency to pinguescence. One article after another in the diet must be left out till a fair balance of nutrition is permanently secured. For an adult in early and middle life the relative quantities of food required should average 12 to 14 ounces of meat, 6 to 8 ounces of toasted bread, casein bread, rusk, or gluten and almond biscuit, 4 to 5 ounces of green vegetable, 1 to 1½ ounce of butter and fat, and 30 to 35 ounces of fluid, including wine, tea, and water. As a disciplinary measure it is proper to measure and weigh the food at the outset of treatment. This method also prevents an insidious tendency

to excess in some articles of the dietary. The patient should be weighed, in the same clothing, or better still without clothes, once a week.

Treatment by Diminution of Fluids (Dry Diet).—It is certain that the weight of the body and over-storage of fat can be reduced more or less by a reduction in the amount of fluid consumed. In restricting liquids, as in limiting anything else, there is often great difficulty in securing co-operation and obedience from patients accustomed to self-indulgence, especially if treatment be carried on at home. The plan of restricting fluids may be applied in any case of obesity presenting no contrary indications. In cases with weakness and dilatation of the cardiac walls, in which hydraemia and tendency to dropsy exist, as in the anaemic type of cases, the benefit from a so-called dry diet may be very marked. It is well to limit the fluids of all kinds to thirty ounces, but the amount must vary a little according to the time of year and the particular food taken. Cardiac tonics, such as digitalis, are found to act with more efficiency when restriction of fluids is practised.

This plan is not practicable nor advisable in cases in which glycosuria is present. It may be noted that obesity may long precede the occurrence of glycosuria, and that early treatment for the former may not improbably stave off the latter condition. There appears to be a considerable retention of chlorides in obese subjects. The diminution of fluids as part of the treatment increases the proportion of chlorides in the tissues. With this there is a reaction, and a tendency to retain as much fluid as possible in the system. The amount of urine is diminished. A chloride-free diet is therefore indicated, together with the usual restrictions enjoined.

Increased Water-drinking sometimes Necessary.—More free dilution, especially by water-drinking, is advisable, and indeed necessary, to remove excess of glucose from the system. Not less than three pints per diem may be considered the normal amount of fluid for consumption, and seventy ounces or more may often be taken. Persons of large frame require larger quantities of fluid. Cases of gouty diabetes with corpulence will be benefited by a larger rather than smaller supply of fluid, provided there be no cardiac or renal complications. In albuminuria, which is not infrequently present in obesity, a restriction of fluid is often called for to meet associated cardiovascular difficulties. If proteins be given in large quantity it is necessary to enjoin abundant water-drinking to carry off the products of nitrogenous metabolism, which would otherwise become noxious. This is an essential feature of the Salisbury treatment (Vol. I. p. 244). Fats and carbohydrates are elements of food which induce much less metabolism than protein matters. Protein food increases both protein and non-nitrogenous metabolism, and may thus reduce the fat of the body. The gouty habit, with lithaemic tendency, if associated with obesity, demands free dilution. In all these conditions it is proper to take fluids freely about three hours after the larger meals, and not with them. Half a pint of cold or hot water may be also taken early in the

morning and late at night. Water taken into an empty stomach is nearly all passed on to the duodenum, but little apparently seems to be absorbed from the gastric surface. To drink freely of water certainly increases metabolism, more urea being discharged than can otherwise be accounted for. If the skin act freely, as often happens in obese persons, more fluid will necessarily be demanded.

Treatment by Spa Waters.—Certain spas are in repute and much resorted to for the treatment of obesity. The springs of Carlsbad and Marienbad are well adapted for many cases. The plethoric form of obesity is that in which most benefit is likely to accrue. Hot alkaline sodium sulphate waters are available at the former, and cold ones at the latter spring. At Carlsbad there are many supplementary measures available for diminishing corpulence : hot mineral, mud, and vapour baths, massage, gymnastics, and electricity are within easy reach of the patient. The functions of the skin, muscles, and gastro-intestinal tract are all stimulated, and active metabolism encouraged.

The Marienbad course is more bracing. The dietary is well arranged, and a general disciplinary regimen is admirably carried out which is commonly very desirable for obese patients yet difficult to secure to the same extent in other watering-places. This course is not desirable in the case of patients with cardiovascular derangements, nor in the anaemic class of obese persons. No routine course is, however, pursued, and under skilled medical supervision, there is no need to fear that any injury may be done by over-treatment.

When a milder course appears desirable, it may be carried out at Homburg, Ems, Kissingen, Tarasp, or Brides-les-Bains. It is often asserted that the special advantages of spa treatment are but temporary. This need not be the case. An obese patient may be set on a right course, but he must continue to pursue it under medical guidance, and carry out the particular diet and habits necessary for his peculiar condition. Relapses are only too common under any method of treatment unless due and permanent precautions are taken. Oertel lays great stress on regulated exercises, such as the gentle climbing, especially in mountain districts, known as the "terrain" cure. He regards spa treatment alone as no specific in these cases, but only adjuvant to other measures, and even harmful when overdone or carried out so as to starve the patient. It is well to repeat visits to such spas as are found suitable whenever possible. In anaemic cases aperient waters containing a little iron are of especial value. Where there is any cardiac weakness or dilatation great care is necessary in enjoining any but very gentle spa treatment, and the fluids should be restricted. The same rule holds good where arterial sclerosis prevails.

If glycosuria is present, Carlsbad treatment, or that pursued at Neuenahr, is advantageous ; and the same may be said in respect of the multiform phases manifested by a gouty proclivity.

Roman or Russian vapour baths are available in cases presenting hydraemia, when restriction of fluids is called for. Not more than three

baths should be taken in each week while undergoing treatment. Cardiac disturbances may be aggravated by vapour baths.

It is stated by Lahnsen that there is an absolute immunity from obesity on the sea-coasts. This is, perhaps, too general a statement, but there is probably a basis of truth in it, and a seaside residence may be recommended with advantage in some cases of strong predisposition to obesity. Persons of gouty inheritance, many of whom are disposed to undue corpulence, are not, as a rule, well affected by marine influences, and enjoy better health inland, in hilly and breezy countries.

Treatment by Thyroid Extract.—Some satisfactory results have been obtained of late in the treatment of obesity by the use of thyroid extract, conjoined with prudent dietetic measures. There can be no doubt that this agent has a very marked influence on the nutrition of the skin and integumentary system generally. There is, as yet, however, no certain knowledge as to the particular class of cases in which benefit may be expected. Hence it is not advisable to resort to such treatment indiscriminately. Ebstein has found that loss of weight under its use is inconstant, and does not recommend it. Young persons of both sexes shew no falling off in weight even after some months of thyroid treatment. The best results have occurred in females between the ages of 25 and 45 years. In males of these ages the results are uncertain. It is alleged that no special alteration of diet is called for while undergoing this treatment, but alcohol should be withheld. That thyroid medication is universally applicable can hardly be expected; but it may sometimes prove serviceable in default of other well-recognised methods of treatment, or in addition to them. In any case it must be used with the same strict precautionary measures as are necessary in treating patients for myxoedema. Five to ten grains of thyroid extract in tabular form may be given best at bedtime when thought advisable. Mr. Chune Fletcher has related to me some excellent and encouraging results in the anaemic class of cases, especially in women of middle age. It is probable that in some of these cases there is a measure of thyroidal inadequacy without obvious atrophy of the gland, suggestive of premature glandular involution.

LOCALISED FORMS OF OBESITY.—*Symmetrical Adeno-lipomatosis.*—This variety appears to be almost confined to males. There is commonly an alcoholic history. The enlargements occur chiefly in the neck, giving rise to double or triple chin, submaxillary and parotid tumours. They are met with over the mammae, recti abdominis, pubes, and inguinal regions. The perineum and scrotum may be the seats of them. They are in evident connexion with the lympharia, and there may be dilatations of related lymphatics. More than 80 cases have been recorded. The tumours may begin after 20 years of age. The disorder is probably allied to the diffuse form of lipoma and to Dercum's disease.

Cervical Adeno-lipomatosis of Tuberculous Origin.—This condition is not generally recognised, and has not been described in British literature. It consists of tuberculous glands invested by masses of fat, and occurs only

in the submaxillary and cervical regions. It may give rise to the appearance of a double chin. No fatty tumours occur elsewhere. Virchow observed that tuberculous glands may be a starting-point of lipoma, and it has been suggested by Labb   that a local lipomatosis may represent an effort of nature to localise the disease.

These tumours appear to be more common in males.

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D. D.

ADIPOSIS DOLOROSA

By Sir DYCE DUCKWORTH, M.D., LL.D., F.R.C.P.

THIS peculiar condition, sometimes spoken of as Dercum's disease, as it was first described in 1888 by Dercum of Philadelphia, consists in the deposit of fatty masses in various parts of the body, sometimes symmetrically, sometimes irregularly, which are preceded or attended by pain.

Etiology.—Little is known as to the etiology. The condition appears in part to be connected with polyneuritis, and the anaesthetic areas sometimes noted afford further evidence in favour of nervous derangement. This painful variety of obesity may be regarded as neurotrophic in character. The thyroid gland was the seat of morbid changes in six out of the seven cases examined (Guillain and Alquier), the case in which it was healthy being one of Dercum's. Degeneration, calcareous change, and atrophy of the thyroid gland, have been recorded amongst the few necropsies, and the pituitary body was notably altered in the two cases

(Dercum, Guillain and Alquier) in which it was examined, thus suggesting some possible toxic influence or perverted metabolism. In some cases there has been noted a history of alcoholism, rheumatism, or of syphilis. It is met with chiefly in women, being four times commoner in them than in men, and occurs in middle life or later.

Morbid Anatomy.—The face, hands, and feet are not affected. The deposits vary in size, some may become very large. They are often tender to the touch, and there may be severe burning and paroxysmal pains in them. The sites of election appear to be the back, at the junction of the back and neck, the posterior aspects of the arms, the upper part of the thorax, and the anterior and external aspects of the thighs. Sometimes in the diffuse form, the whole subcutaneous tissue is inflated with a layer of fat of variable thickness, resulting in the most striking deformity of the limbs, which may be hardly recognisable as limbs. It is curious that this infiltration usually stops at the terminal articular folds of the limbs.

Varieties.—Three forms of this disorder have been noted: (1) The lipomatous; (2) the localised fatty; and (3) the diffuse fatty. In the first, sometimes described as the nodular form, there are fatty tumours varying from the size of a nut to that of a tangerine orange. The second variety may follow on the nodular form, the fat terminating sharply at the wrists and ankles, so that the hand appears to come out as from a cuff, and the foot from a pantaloons. In the third form there is a general obesity with pain.

Various associated conditions have been observed in these cases. There is commonly more or less asthenia and psychical disturbance. Haemorrhages occur in the form of epistaxis, menorrhagia, haematemesis, and petechiae. Ocular paralysis and sensory disturbances, such as deafness, diminished sense of smell and taste, have been noted. Once started, there appears to be little or no remission in the course of the disorder. Marked muscular weakness and the reaction of degeneration have been noted by Dercum.

Treatment is empirical and not always satisfactory. Iodine, strychnine, electricity, and hydrotherapy have been employed, but have merely afforded temporary relief. The discovery of thyroid inadequacy in several of these fatal cases has suggested the employment of thyroid extract. Debove was not satisfied with its efficacy in his patients. Mr. Chune Fletcher, however, informs me that he has had distinctly favourable results in several cases both of the diffuse and localised varieties of this disease. These have occurred in women of middle age, and the treatment has been of especial value in cases in which the fatty masses form, as they are wont to do, on the supraclavicular, inframammary, and lower scapular regions. Thyroid tablets should be given at bedtime in doses of 5 to 10 grains, and continued for months. The fatty masses disappear, and the general health is markedly improved. When the treatment is suspended the masses are apt to re-form. No ill-effects of any kind have been noted from a continuance of this medication. The pains may possibly yield to doses of phenacetin, or aspirin, or be mitigated

by local applications of aconite and belladonna. Morphine may sometimes be necessary.

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D. D.

OEDEMA

By W. D. HALLIBURTON, M.D., LL.D., F.R.S.

SYNOPSIS.—The Physiology of Lymph-formation and Absorption—The General Pathology of Oedema-formation—The Chemical Characters of the principal Kinds of Dropsical Fluids—Cytology.

The Physiology of Lymph-formation and Absorption.—The blood does not come into direct contact with the tissue-elements which it ultimately nourishes except in the spleen, and in haemal glands similar in structure to the spleen. As it circulates through the thin-walled capillaries a leakage or transudation of fluid takes place. The exuded fluid is termed lymph, and lymph is in normal conditions the intermediary between the blood and the tissue-elements; it conveys to them the oxygen and nutriment they need, and removes from them the waste products of their activity. This fluid passes from the tissue spaces into definite lymphatic channels, and these converge to the main lymphatic trunk or thoracic duct, by means of which the lymph is returned to the blood vascular system.

Certain changes in the circulatory conditions, for instance a rise in the blood-pressure within the capillaries, will cause an increased formation of lymph. In some cases, also, it has been stated that functional activity of certain organs will increase the flow of lymph which leaves them. The actual amount of lymph formed in any particular district of the body is thus subject to fairly wide physiological variations, and an increase is not followed by an accumulation of watery fluid in that

district, because the increased formation is followed by an increase in the normal means the body possesses of keeping the amount of lymph present at a minimum ; more passes into the lymphatics and is thus removed. If these physiological limits are exceeded, then the tissues become bathed in an excess of fluid, and the condition called oedema or dropsy is the result.

In order to understand the pathology of dropsy it is thus necessary to study first the physiology of lymph-formation. Lymph is found on chemical analysis to have a similar composition to blood-plasma. The number of anatomical elements in it is small and limited to corpuscles of the colourless variety, which originate either as wander-cells from the blood-stream, or are added to it by lymphoid and similar tissues through which it passes on its journey back to the heart. The proteins present in the lymph-plasma are the same as those in the blood, namely, fibrinogen, serum albumin, and serum globulin, but the quantity present is much less. Lymph clots when it is shed, but the yield of fibrin is less than that formed in blood-plasma. The salts in lymph and blood are identical both in quantity and kind. The products of waste (for example, carbon dioxide, urea) are more abundant in lymph than in blood.

With regard to the mechanism of lymph-formation, there are two principal views held : one is that its formation is simply due to the operation of physical factors ; the other is that it is formed by the vital or secretory activity of the endothelial cells of the capillaries. Carl Ludwig taught that the lymph flow is conditioned by two factors : first, differences in the pressure of the blood in the capillaries and that of the fluid in the tissue spaces ; this would give rise to the forcing of the constituents of the blood-fluid through the capillary walls, or as it is usually called *filtration* ; secondly, chemical differences between the fluid inside and outside the capillary wall would set up an *osmotic* flow of water. If the lymph is produced by a simple act of filtration, then the amount of lymph must rise and fall with the value of $D - d$; D being the capillary blood-pressure, and d the pressure in the tissue spaces.

As time went on, it was found that certain observed facts were not compatible with such a simple hypothesis ; among other things it was shewn that certain drugs (for instance curare) increased the lymph flow without apparently influencing D or d primarily.

The view that the secretory activity of the endothelium was a factor to be reckoned with gradually forced its way, and culminated in the celebrated work performed by Heidenhain. He found that many substances increased the flow of lymph, and these lymphagogues he divided into two classes : the first class consisted of various organic colloid materials, such as leech extract, decoction of mussels, peptone ; and the second of crystalloid substances, such as sugar and salt. He considered that the majority of these substances acted by stimulating the endothelial cells to greater activity. These views were supported by Hamburger, but have been the subject of much discussion, but it will be sufficient for our present purpose to state briefly the views of Prof. Starling, which

may be taken as typical of those which defend the older mechanical hypothesis. Prof. Starling points out that Heidenhain made a mistake in taking the arterial pressure as his measure of the capillary pressure ; for there is, of course, between the arteries and the capillaries the unknown resistance of the arterioles. He also shewed that besides capillary pressure, the other great factor in the causation of the lymph-flow is the permeability of the capillary wall ; this varies enormously in different regions, being far greater in the liver capillaries than in the limb capillaries. An increase of intracapillary pressure which would cause lymph to flow in the former is often quite ineffective in the latter situation. More protein comes through into the lymph of the liver and intestinal region than is the case in the capillaries of the limbs ; protein is practically non-diffusible, so its pressure in the lymph is explicable only on the filtration hypothesis (if secretory activity is not admitted), and naturally most will come through where the filter is least efficient. If we adopt Prof. Starling's view the flow of lymph may, therefore, be experimentally increased in two ways, and, as we shall see directly, these are also the two principal ways which lead to that abnormal production of lymph which constitutes dropsy. The two ways are : (1) By increasing the intracapillary pressure. This may be done locally by ligaturing the veins of an organ or limb ; or generally by injecting a large amount of fluid into the circulation ; or by injecting such substances as sugar and salt (Heidenhain's second class of lymphagogues), which, in virtue of their osmotic pressure, attract water from the tissues into the blood, and thus increase the volume of the circulating fluid and raise the intracapillary pressure. (2) By increasing the permeability of the capillary wall by injuring its vitality. This may be done locally, as by scalding a part ; or generally, by injecting certain poisonous substances. Heidenhain's first class of lymphagogues comes into this category ; they act chiefly on the liver capillaries ; curare acts chiefly on the limb capillaries.

In the study of oedema, to which we shall pass immediately, we shall see that both these factors may be present, and that often one by itself is ineffective to produce a dropsical state.

This is the view at present favoured by physiologists and pathologists alike, but we should be cautious at present in regarding it as absolutely final. If the endothelial wall were a non-living membrane, physical processes would obviously explain all the phenomena of lymph-formation ; but we must recognise that the endothelial cells are alive, and that, like other cells, they are capable of a selective action which may mask, or counteract, or assist the purely physical processes. If the action of poisons was simply to injure the vessel wall and increase its permeability, the amount of lymph should be proportional to the intensity of the injury, but this is not invariably the case. Lymph-formation is doubtless mainly influenced by the physical conditions present, but at the same time it is impossible to deny that there is some such action as may be described by the terms "selective" or secretory. This question is closely related to that of absorption of food material from the alimentary canal, and here

all recent work tends to shew the importance of the selective action the intestinal epithelium possesses.

The physical processes are the easiest to observe and measure, because the laws that regulate them are known. Secretory activity is regulated by laws also, but the paucity of our knowledge of them prevents any exact estimate of the importance of the selective factor in lymph-formation.

Osmotic Phenomena.—It has been generally assumed that proteins, which are the most abundant constituents of the blood, exert little or no osmotic pressure. It is difficult from the theoretical standpoint to imagine that a pure protein can possess more than a minimal pressure of this kind. It is made up of such huge molecules, that even when protein is present to the extent of 7 to 8 per cent, as it is in blood-plasma, there are comparatively few molecules present, and these are in a state of colloidal solution, not true solution. The proteins, as they exist in the blood, are, however, mechanically combined with certain mineral constituents which they adsorb, and the osmotic pressure they exert is thus explicable. The more they are freed from the inorganic (electrolyte) admixture the smaller is their osmotic pressure. The normal osmotic pressure exerted by the proteins of blood-plasma is given by Prof. Starling as equal to 30 mm. of mercury, and this is of importance, for proteins, unlike salt, do not diffuse readily, and their effect, therefore, remains as an almost permanent factor in the blood. By means of this weak but constant pressure it is possible to explain the fact that an isotonic or even a hypertonic solution of a diffusible crystalloid may be completely absorbed from the peritoneal cavity into the blood. Osmosis, therefore, is a factor to be reckoned with in the absorption of lymph. As an illustration of the way in which it may also play a part in lymph-formation, we may take Asher's statement that increase of activity in an organ will increase the lymph that flows away from it. This is not altogether the result of the hyperaemia (increased blood-flow often associated with vaso-dilatation) that usually accompanies activity. In addition to this, we must remember that the functional activity of the tissue-elements is accompanied by a chemical breakdown of their constituents, the proteins, for instance, being in small measure resolved into sulphates, phosphates, and urea precursors. The main source of energy in an active tissue is, however, the non-nitrogenous material, carbohydrate and fat, which are ultimately oxidised into carbon dioxide and water, lactic acid and lower fatty acids being intermediate stages. The products of action pass into the lymph and increase its molecular concentration and its osmotic pressure; thus water is attracted from the blood to the lymph, and so the volume of the lymph rises and its flow increases. Such an effect can only be temporary, for in time these substances attain a greater concentration in the lymph than in the blood, and so they will diffuse towards the blood, by which they are carried to the organs of excretion.

General Pathology of Oedema.—We can now pass on to a study

of those conditions in which the normal balance between lymph production and lymph absorption is upset, and which will bring about, or help to bring about an abnormal distension of the connective-tissue spaces with lymph. Prof. Starling classifies the factors concerned in the causation of dropsy in the following useful table :—

I. Factors causing increased transudation—

- (1) Increased intracapillary pressure, especially that produced by venous obstruction. Vaso-dilatation and plethora are factors of minor importance.
- (2) Increased permeability of the vessel wall, produced by local irritants, malnutrition, or poisons circulating in the body generally.
- (3) A watery condition of the blood (*hydraemia*).

II. Factors causing diminished absorption, either by lymphatics or blood-vessels.

In all cases, however, as Cohnheim pointed out many years ago, the primary cause of oedema is an increased transudation. The normal mechanism of absorption may for some time be able to cope with this, but if the increase of transudation lasts for any length of time, subsidiary events lead to a breakdown of the absorbing mechanism. The cases in which the primary cause of the oedema is diminished absorption must be exceedingly rare. Obstruction of the lymphatics is usually impossible on account of their multitudinous anastomoses, and when complete obstruction does occur, the result is more usually a general hypertrophy of the connective tissues (*elephantiasis*) than a true oedema. From these general data we will now go on to consider the different varieties of oedema which are recognised by clinical observers.

1. *Oedema of Engorgement*.—The determining factor of this kind of dropsy is passive congestion, or a rise of intracapillary pressure. It may be local, as when the veins coming from a special district are compressed by a new growth, or when a vein is the seat of thrombosis, as in "white leg." It may be more or less general when the vein which is compressed is a large and important one, for instance the inferior vena cava. The oedema due to chronic cardiac disease is usually attributed to back pressure, and this will be most effective in causing an engorgement of the general venous system, and so of producing general oedema when the tricuspid valve becomes incompetent. In such cases the oedema usually appears first in dependent parts, that is, in parts such as the feet and ankles, where the hydrostatic effect of gravity is most felt. But, as already stated in our study of lymph-formation, a mere increase of intracapillary pressure will not in itself cause dropsy. Ligature of even a large vein in the limb of a healthy animal will not produce oedema of the limb. This is owing to the collateral circulation carried on by other veins; all the veins from a limb must be ligatured or obstructed in some way to cause dropsy. If, however, the vitality of the animal is reduced by anaemia (for instance, by bleeding), the endothelium will share in the depression, it will become more

permeable, and then ligature of a single large vein will produce dropsy.

Venous obstruction seldom affects all the veins of a limb, but yet venous obstruction will cause the limb to become oedematous. No doubt the damming back of the blood in the capillaries prevents their endothelium from obtaining their usual supply of oxygen, and the effect of this partial asphyxiation is so to injure it, that it becomes more permeable and so allows of an increased leakage of fluid. In heart disease, as Prof. Starling has shewn, the increase of intracapillary pressure is also unable to produce oedema, unless at the same time the endothelium of the capillaries has been damaged by a diminution of the circulation through them. This is true, not only for the limbs, but also for effusion into the serous cavities. Increase of capillary pressure will not produce hydrothorax in a healthy animal, but if the endothelium is first damaged by the injection of a poison (for example, abrin, the poisonous protein of the Jequirity bean), then hydrothorax is readily produced. In the peritoneal cavity, damage to the capillary walls in the intestine can be easily effected by immersing the intestinal coils in tap-water for a few minutes, and then a rise of intracapillary pressure will produce ascites ; but if the permeability of the capillary wall is normal, such a rise of pressure is ineffective. The hepatic capillaries are normally more permeable than those in most other parts of the body, so comparatively slight damage to them will cause the physiological limit to be exceeded, and this, no doubt, is the reason why ascites is such a common form of dropsy. Dr. C. Bolton has made a more recent study of dropsy produced in animals by obstruction of the vena cava and portal vein. He has arrived at the conclusion that it depends entirely upon an altered condition of the capillary wall, and that raised capillary pressure and an altered condition of the nutrition of the tissues (as maintained by Dr. Lazarus-Barlow) are unimportant factors.

The dropsy of heart disease is, however, not merely the result of the causes already mentioned, but other forces come also into play : the blood becomes more watery owing to continued absorption from the alimentary canal and diminished excretion from the kidneys ; and there is another complication not present in simple venous obstruction, and that is a diminished outflow from the lymphatics in consequence of the raised venous pressure at the orifice of the thoracic duct. The sequence of events in cases of heart disease with inefficient compensation may be divided into the following four stages (Starling) :—(1) Failure of the heart as a pump, leading to a fall of arterial pressure, and a rise of pressure in the large venous trunks near the heart. Accompanying this is a fall of capillary pressure, and a consequent increased absorption of fluid from the intestines and tissues generally into the circulation, with a diminished production of urine. Stage 2 is that of hydramic plethora, and is a consequence of the first stage ; this leads to a rise of the mean pressure throughout the vascular system. Stage 3 is the stage of dropsy, caused by the high capillary pressure, and the increased permeability of

the capillaries owing to malnutrition. Stage 4. The continued hydraemic plethora leads to ever-increasing over-filling of the heart cavities, and to ultimate failure of the already incompetent heart.

Ascites in hepatic cirrhosis has been in the past attributed to compression of the portal vessels by the new growth of connective tissue. This hypothesis has, however, been formulated more as a matter of inference than as a result of direct observation and experiment. A research carried out by Dr. F. C. Herrick at the London Hospital has shewn that the conception has no foundation, but that the increased pressure in the portal capillaries has a very different origin. There is absolutely no evidence of obstruction from fibrosis either in the portal or hepatic veins. The arterial supply to the fibrous tissue is increased, the capillaries there are dilated, and thus more fluid passes through the arterial capillaries into the portal venules. In the normal liver the pressure in the portal capillaries is low, because they have behind them mainly the low pressure of the portal vein. In the cirrhotic liver, on the other hand, the high arterial pressure is readily transmitted to them, and so the intracapillary pressure is correspondingly raised. This is accentuated if the hepatic veins are not quite able to give passage to the increased volume of fluid, and any weakening of the heart would favour this backward pressure. This is quite sufficient to explain logically the high intracapillary pressure ; if, however, we accept the dictum of Prof. Starling and of Dr. Bolton on the importance of an increased permeability of the capillary wall in dropsy-formation, this second factor may be accounted for by the increased strain to which the capillaries are subjected, and probably also to the circumstance that their nutrition is below normal, owing to the blood not being absolutely healthy ; it is difficult to imagine a serious interference with liver function producing no ill effects on the circulating fluid.

2. *Hydraemic or Cachectic Dropsy*.—This is typically seen in renal disease and in anaemia. It is also seen in many other chronic affections, such as diabetes, cancer, tuberculosis, which may or may not be associated with anaemia ; in all such cases there are poisons circulating in the body. In these conditions the site of the oedema is not much affected by gravity. In renal disease, for instance, puffiness of the skin is usually first seen in the face. In renal disease, however, the later stages are often complicated by cardiac failure, and so the dropsy may have a double causation. The old view that in such cases the dropsy is due to an increase of water in the blood (hydraemia) cannot be considered tenable any longer, for hydraemia artificially induced in health does not produce dropsy. Dr. Lazarus-Barlow, who has worked mainly on the question of the part osmosis plays, speaks of the condition as one of tissue-starvation ; waste products accumulate, stimulate the secretory activity of the endothelium, and so excite a flow of lymph in excess of the normal. Whether the poison acts in this way, or by injuring the vitality of the endothelium, and so increasing its permeability, or of setting up an osmotic flow of water, is at present uncertain. There is, however, no doubt as to the

necessity of a poison acting in one or more of those ways, and in renal disease it is possible that the poison is the same as that which produces an injury of the renal epithelium. The almost constant appearance of dropsy in the region of the eyelids in renal disease appears to indicate that the capillaries in this region are specially vulnerable ; and this view is to some extent supported by the frequency with which urticaria attacks the face. Beriberi is another disease in which oedema is a notable symptom. Here again the action of some at present unknown poison is at work (*vide Vol. II. Part II. p. 622*), though in the latter stages of the disease cardiac failure will assist in the production of dropsy.

3. *Inflammatory Oedema*.—This is a local oedema of which injury to the vessel-walls from stasis and action of bacterial poisons is the obvious cause. The exuded fluid is rich in protein in comparison with other forms of dropsical fluid. It is also rich in colourless corpuscles, and it is to this circumstance that its ready coagulability is due. It clots rapidly when removed from the body, and fibrin-formation may also occur in it *in situ*.

4. *Lymphatic Dropsy*.—This is due to occlusion or pressure upon the larger lymphatic trunks, such as the thoracic duct. If rupture of such vessels occurs chylous ascites is the result ; or if the rupture occurs in the thoracic region chylous hydrothorax follows. A special cause of obstruction in lymphatics is the presence of filaria embryos, as in various forms of elephantiasis ; or if a connexion is established with the urinary tract chyluria follows. The most obvious sign of admixture with chyle is the rise in the amount of fat present. The fat-droplets are visible under the microscope. Fairly frequently ascitic fluid has an opalescent or milky appearance, but neither microscopic examination nor chemical analysis reveals the presence of an increase of fat. The cause of this appearance is far from clear ; it is not due to admixture with chyle ; nor is it associated with a lipaemic condition of the blood which is occasionally seen in such diseases as diabetes. The opalescence is due to the proteins the fluid contains, but we do not at present know whether the usual blood-proteins altered in some direction are responsible for the cloudiness, or whether some foreign protein (perhaps allied to the mucoids presently to be mentioned) is present.

5. *Oedema associated with Angioneuroses*.—The oedema seen in some cases of exophthalmic goitre, and the localised oedema of urticaria and erythema nodosum, come under this heading. The onset of swelling in such cases is often extremely rapid. The ultimate causation of the oedematous condition is obscure, and is usually attributed to nervous influence. The nervous system has no action, so far as is known, on endothelium, and so the effect must be of vasomotor nature. The so-called meningeal streak or tache cérébrale is a phenomenon of similar nature. No doubt in some of the instances mentioned the presence of a poison is a contributory cause of the oedema. This is notably so in urticaria. A deficiency of coagulative power in the blood, Sir A. E. Wright states, is sometimes present, but it is difficult to see how this in

itself can produce increased leakage of lymph, although it may be an indication that the blood is not in a normal state, and so not likely to maintain the proper nutritional condition of the endothelium.

6. *Myxoedema*.—This name was originally given to the disease in question on the supposition that excess of mucin in the subcutaneous tissues is the cause of the swelling. There is doubtless an overgrowth of the subcutaneous connective tissue, and in early stages such tissue, like all young connective tissue, is comparatively rich in ground-substance and therefore in mucin. Even at this stage it requires very careful analysis to demonstrate the increase; and in later stages, when the matrix of the tissue becomes pervaded with fibres and mixed with adipose tissue, there is no increase in mucin at all. The term myxoedema, in fact, is a misnomer.

7. *Dropsical Conditions in the Cerebrospinal Cavity*.—The cerebrospinal fluid plays the part of a lymph in the central nervous system, but it differs in its mode of formation and composition from ordinary lymph. All observers agree that it is a real secretion, primarily formed by the epithelium covering the choroidal plexuses. To it are added the products of metabolism of the nervous tissues. In cases of meningocele and hydrocephalus, the fluid present is cerebrospinal fluid differing but little, if at all, from the normal fluid. If inflammation supervene, the characters of the fluid may be masked by admixture with the exudation of ordinary inflammatory oedema. The relations of the cerebrospinal fluid in health and disease are of the utmost importance and interest, but as they do not come into the present question, will be treated separately in connexion with the general pathology of the Nervous System (Vol. VII.).

Chemical Characters of Dropsical Fluids.—We may take the normal fluids as a standard of comparison:—

1000 Parts of Human Blood-Plasma contain	1000 Parts of Human Lymph (from thigh) contain
Water	986·34
Solids	13·66
Yield of fibrin	1·07
Total protein	3·40
Urea	0·16 to 0·21
Extractives	1·31
Inorganic salts	8·78

If a = percentage of albumin, and b = that of globulin, then a/b is called the protein-quotient. This varies considerably in different animals, but in the same animal it is the same in serum, lymph, and chyle.

The following table, somewhat abbreviated from Hoppe-Seyler, gives the composition of chyle in parts per 1000:—

Constituents.	Chyle of Dog.	Serum of same Dog.	Human Chyle.	Human Chyle (Schmidt).
Water . . .	906·77	936·01	904·8	943 to 958
Solids . . .	96·23	63·99	95·2	57 to 42
Yield of fibrin . .	1·11
Total protein . .	22·16	45·24	70·8	11 to 13
Fat, lecithin, and cholesterin . .	64·86	6·81	9·2	25 to 27
Fatty acids and soaps . .	2·34	2·91	10·8	..
Other organic substances . .	7·92	8·76	4·4	6·25

The most striking points in a comparison of the lymph from a limb and the chyle are, the high percentage of fat and the high percentage of protein in the chyle. The latter circumstance is due to the greater permeability of the capillaries in the abdominal and thoracic regions.

General Properties of Dropsical Fluids.—The reaction is in all cases alkaline to litmus; the colour varies directly with the colour of the blood-plasma, and the concentration of the effused fluid; there is always present a certain amount of the yellowish lipochrome (serum lutein) found also in the blood. In some cases this may be obscured by opalescence as already explained.

The specific gravity varies with the amount of solids in solution. Reuss has examined a large number of dropsical fluids; those of inflammatory dropsy he terms exudations; those from non-inflammatory dropsy, transudations. The following are his conclusions in reference to specific gravity:—

Fluids from cases of peritonitis,		1018 or higher	exudations.
" " pleurisy,	1018	"	
" " inflammation of skin,	1018	"	
" " hydrothorax,	1015 or lower		transudations.
" " ascites,	1012	"	
" " oedema of skin,	1010	"	

Coagulation.—The inflammatory fluids contain abundance of colourless corpuscles, and invariably clot when shed. In cases where they clot within a serous cavity, the fibrin (often termed lymph in the post-mortem room) sticks to the sides of the membrane. Non-inflammatory fluids do not coagulate spontaneously, or only with great slowness. This is due to absence or paucity of formed elements. On admixture with fibrin-ferment (thrombin) or fluids such as serum which contain thrombin, clotting ensues.

Constituents.—These are the same in kind as those in the blood-plasma. (a) Proteins. These are fibrinogen, serum-globulin, and

serum-albumin. (b) Extractives. A large number of organic substances, each usually in small amount, are included under this head. Sugar is a fairly constant constituent. (c) Salts, similar in kind and amount to those in the blood. The different dropsical fluids differ from one another in their richness in organic constituents, the substances which vary most being the proteins. In general terms, if transudations are formed in several situations in the same person the pleural fluid is richest in protein, then the peritoneal, and lastly the fluid of subcutaneous oedema. This has been shewn over and over again by various observers; but it will be sufficient for our purpose to quote one typical case in illustration of this point:—

**FLUIDS REMOVED SIMULTANEOUSLY FROM A CASE OF ALBUMINURIA
(Hoppe-Seyler).**

In Parts per 1000.	Pleural Fluid.	Peritoneal Fluid.	Fluid of Subcutaneous Oedema.
Water	957·59	967·68	982·17
Solids	42·41	33·32	17·88
Proteins	27·82	16·11	3·64
Extractives and salts	14·59	16·21	14·16

The protein-quotient remains the same in the effusions as in the blood of the same individual. That is to say, although the amount of protein exuded varies, the two principal proteins of the blood come through in approximately the same proportion that they bear to one another in the blood. Again, one typical analytical table (from Pigeaud) will be a sufficient illustration of this:—

Fluid.	CASE 1.		CASE 2.	
	Total Protein per cent.	Protein-Quotient :— Albumin. Globulin.	Total Protein per cent.	Protein-Quotient.
Blood-serum . . .	5·261	0·664	5·781	1·056
Pleural fluid . . .	0·808	0·680	0·900	1·142
Ascitic fluid . . .	0·452	0·686	0·832	1·122
Subcutaneous oedema fluid . . .	0·212	0·687	0·775	1·152

In many cases in the progress of a dropsy it is necessary to tap the cavity several times. It is then found that successive dropsical transudations into the same sac usually present great constancy of composition. If, however, inflammation be set up as the result of imperfectly cleaned

instruments used in the tapping, then of course the quantity of protein in the effused fluid rises.

Peritoneal Fluid.—Although in the foregoing account of dropsical fluids some details have already been presented in relation to the fluid found in the peritoneum, it is necessary to go a little more fully into certain other points. These may be conveniently stated in the form of propositions, each of which is followed by an illustrative analysis.

1. The fluid removed from the peritoneal sac by successive tappings remains fairly constant in composition.

CASE OF CIRRHOSIS OF LIVER (Hoppe-Seyler).

In Parts per 1000.	First Tapping.	Second Tapping.	Removed after Death.
Water	984·50	982·53	983·33
Solids	15·50	17·47	16·67
Proteins	6·17	7·73	6·11
Extractives	1·25	1·84	3·25
Salts	8·46	8·13	8·24

2. The amount of protein in different cases is variable. This may be illustrated by the following analyses selected from a larger number made by myself :—

Case.	Specific Gravity.	Total Protein per cent.	Serum Globulin.	Serum Albumin.
1. Cirrhosis of liver	1010	0·955	0·413	0·542
2. Syphilitic disease of liver	1012	0·744	0·252	0·492
3. Cirrhosis of liver	1012	2·021	1·114	0·907
4.	1016	2·235	1·516	0·719
5. Heart disease	1016	4·11	1·480	2·630
6.	1018	4·334	2·937	1·397

The percentage of protein in transudations from heart disease is usually high, and that gives point to what has already been said in reference to this variety of dropsy not being simply the result of back pressure. Many years ago, Wooldridge, struck with this, supposed that an altered condition of the blood might account for it; but no blood-poison has been definitely proved to be present.

3. In the same case, the total protein and the protein-quotient (albumin : globulin) remain very constant; and in cases in which, owing to alterations of pressure or changes in the permeability of the endothelium, the total protein varies in amount, yet the quotient is but slightly altered. (See next table.)

CASE OF CIRRHOSIS OF THE LIVER (Pigeaud).

Date of Tapping.	Total Protein per cent.	Protein-Quotient.
July 20 . . .	3·285	1·483
August 25 . . .	0·632	1·573
September 30 . . .	2·368	1·532
November 15 . . .	3·216	1·525
December 27 . . .	2·688	1·486

4. The total protein in the fluid in cases of peritonitis is increased as compared with that of simple non-inflammatory ascites. Runeberg from the examination of 121 cases gives the following general results :—

	Percentage of Protein.
In cases of hydraemia (including nephritis) the ascitic fluid contains	0·03 to 0·41
In cases of portal obstruction	0·37 to 2·68
" heart disease	0·84 to 2·3
" peritonitis	2·7 to 3·51

In some cases of ascites the fluid contains excess of cholesterin, crystals of which are seen floating in it. In other cases the peculiar mucoid substances variously termed metalbumin (or pseudo-mucin) and paralBUMIN are found. The presence of these mucoids is attributed to a kind of "colloid" degeneration, and in "colloid cysts" of the ovary they are constant constituents of the contents of the cysts. Drs. Miller and Wynn have very thoroughly described one of these cases of mucoid ascites. In this case the mucoid material originated from a degenerative change in the cells of a tumour which grew from the endothelium of the peritoneum.

In another class of cases of ascites, haemorrhage may occur into the peritoneum, and the liquid is more or less stained with blood or altered blood pigment.

Chylous ascites is another modification that may occur, and I append analysis of two cases, in the first case performed by M. Hay, in the second by Guinochet :—

Constituents.	Parts per 1000.	
	I.	II.
Total solids	59·15	43·79
Fat	10·30	9·48
Protein	28·78	21·08
Other organic substances	8·02	11·68
Salts	9·95	1·59

For a consideration of the chylous, chyloform, and milky non-fatty forms of ascites, see "Diseases of the Lymphatic Vessels" in Vol. VI.

Pleural Fluid.—This fluid has the same general characters as peritoneal fluid, but is usually richer in proteins. In hydrothorax the protein is less abundant than in pleurisy. The next table (from my own analyses) illustrates this point:—

Case.	Specific Gravity.	Total Proteids per cent.	Yield of Fibrin.
1. Acute pleurisy	1023	5·13	0·016
2. " " " " "	1020	3·44	0·017
3. " " " " "	1020	5·20	0·10
4. Hydrothorax (Bright's disease)	1015	2·52	0·006
5. " " " " "	1012	1·32	0·006
6. Hydrothorax (heart disease) .	1016	1·48	0·013

In hydrothorax, as in ascites, the fluid removed by successive tappings remains fairly constant in composition; this is illustrated by the following analyses by C. Schmidt:—

Constituents of Hydrothorax Fluid.	First Tapping.	Second Tapping.
	Parts per 1000.	Parts per 1000.
Water	966·24	963·95
Solids	33·76	36·05
Organic solids	26·12	28·50
Salts	7·64	7·55

Exceptional conditions are found in pleural as in peritoneal fluid, such as a haemorrhagic condition, a chylous condition, or the presence of excess of cholesterol. Sugar is almost constantly present as in other effusions.

Pericardial Fluid.—Fairly large amounts of this fluid can be obtained post-mortem from the horse; this may serve as a standard to which that obtained from man in dropsical conditions of this serous sac may be compared, as in the following table:—

In Parts per 1000.	Pericardial Fluid of Horse.	Human Pericardial Fluid (8 cases).	Chylo-pericardial Fluid (Hasebroek).
Water	957·9 to 964	955 to 962	892·78
Solids	35·9 to 42	38 to 45	103·61
Fibrin	0·12 to 0·26	0·8	...
Total protein	25·8 to 28·6	22·8 to 24·7	73·79
Extractives	2·43	12·7	20·48
Salts	7·6 to 13	6·7	9·37

In the case of the chylous effusion into the pericardium above mentioned, more than 50 per cent of the extractives consisted of fat.

The higher percentage of protein in both pleural and pericardial fluid apparently indicates that the capillaries from which the effusion leaks are as permeable, or even more so, than those of the liver, but experimental evidence in this direction is at present lacking.

Hydrocele Fluid.—The tunica vaginalis is in origin a part of the peritoneum, and the fluid itself is almost exactly like the peritoneal fluid.

Its specific gravity varies from 1016 to 1022. The amount of protein it contains varies a good deal. The following is a mean of 17 analyses by Hammarsten :—

Water	938·85	parts per 1000.
Solids	61·15	" "
Total protein	49·25	" "
Yield of fibrin	0·59	" "
Ether-extractives	4·02	" "
Salts	9·26	" "

There are cases which differ from the ordinary fluid; some are viscous from the presence of pseudo-mucin; some contain excess of cholesterol, and others may be chylous. Lymph-tumours and tumours filled with chyle are very common in the scrotum and its neighbourhood in cases of chyluria, and these may discharge their contents on the surface of the skin.

The Fluid of Subcutaneous Oedema.—This fluid is the poorest of all the dropsical fluids in protein; otherwise it resembles them very closely. Some analyses have already been given of this fluid in the comparisons we have drawn between it and other effusions. The following are a few of the estimations of the protein constituents which I have made. In all cases the fluid was obtained from the ankles.

Case.	Specific Gravity.	Total Protein per cent.	Yield of Fibrin.	Serum-Globulin.	Serum-Albumin.
1. Cardiac dropsy . .	1012	0·33	0·0028
2. " " " . .	1013	0·59	traces	0·139	0·453
3. Bright's disease . .	1009	0·64	traces	0·191	0·449

In all cases the fluid which drained away first, coagulated spontaneously on standing; this was due to slight admixture with blood. After haemorrhage had ceased, coagulation did not occur until some fluid containing fibrin-ferment (such as serum) was added. Sugar as usual was almost constantly present.

Blister fluid has the same relation to oedema fluid as that of peritonitis or pleurisy to simple dropsies into the serous cavities. It contains a large number of leucocytes, coagulates spontaneously when drawn, has a higher specific gravity (1018 or more), and a larger percentage of protein, as is

seen by boiling it, when it becomes almost solid from the heat-coagulum produced.

Electrolytes in Pathological Effusions.—So far we have considered mainly the organic constituents of these fluids. The saline constituents are usually similar to those found in the blood, but recent work by O. C. Gruner has shewn that this is not invariably the case. His investigation is on the lines of physical chemistry, and the principal method he employed is that of electrical conductivity. He finds that transudations (non-inflammatory effusions) contain an excess of sodium chloride over achloride electrolytes (Bugarsky and Tangl's classification); this, as is well known, is also true for the blood. Inflammatory effusions or exudations on the other hand contain a relatively smaller amount of chlorides; the increase of achlorides is attributed, probably correctly, to the destruction of the numerous cells such fluids contain. The fluid of ovarian cysts usually contains more achlorides than chlorides. The total conductivity of all the fluids was found to be remarkably constant.

During the last few years, Widal and Javal and other French writers have drawn attention to the relation between dropsy and the retention of chlorides in the tissues. An excessive ingestion of chlorides may even in health lead to an increase of body-weight owing to the tissues retaining more fluid than under normal conditions. When kidney disease is present and the due elimination of chlorides is thus interfered with, the abnormal retention of chlorides in the tissues may according to this view lead to the production of anasarca. One case has been recorded by J. H. Bryant in which this culmination was reached in a perfectly healthy man; this man consumed between 300 and 600 grains (20-40 grams) of salt per diem, and his urine contained about three times the normal quantity of sodium chloride. Oedema occurred in the legs, the explanation put forward being that the kidneys were unable to deal successfully with so much salt, and the consequent accumulation of the salt in the tissues led to the retention of so much water there as to produce an oedematous condition. In this case the dropsy disappeared when the amount of salt in the food was reduced within moderate limits. Widal and Javal found that doses up to 150 grains (10 grams) did not give rise to oedema in cases of interstitial nephritis, but in cases of parenchymatous nephritis such doses produced this effect; the oedema became less or disappeared when the amount of salt in the food was reduced.

The foregoing account of the dropsical fluid relates to all the principal varieties found, but it by no means includes all the possible cases in which accumulation of so-called serous fluids may occur.

Aqueous humour is very dilute lymph (1·3 per cent of total solids).

Perilymph and *endolymph* of the internal ear. Perilymph contains 2·1 per cent of solids including mucin. Endolymph is clearer and less viscid; it contains 1·5 per cent of solids.

Synovia contains from 3·4 to 7·1 per cent of solids. Its viscosity is due to mucin (Landwehr) or to a viscous nucleo-protein (Hammarsten).

The fluid of ovarian cysts is usually viscid from the presence of pseudo-

mucin ; it is often coloured by a brown derivative of haemoglobin, and often contains excess of cholesterol.

The fluid in hydronephrosis is dilute urine mixed with a serous effusion.

The fluid in hydatid cysts is usually a dilute lymph containing 1-3 per cent of solids. It may contain the hooklets of the embryo parasite, and if it escapes into the peritoneal cavity, it is said to set up peritonitis ; some observers have stated it contains a poisonous ptomaine. If the cyst has invaded organs and induced rupture of blood or bile vessels, the fluid obtained will be mixed with blood or bile respectively. In one case which I examined the fluid consisted of little else but bile. In a case recorded by Kaiserling the inspissation of the bile within a hydatid cyst led to the formation of a softish calculus which consisted mainly of bilirubin and fatty matter.

The amniotic fluid is a very watery exudation (percentage of solids 1-5 to 1-8) from the fetal and maternal tissues, diluted in the later stages of pregnancy by fetal urine. In hydramnios the protein matter is increased. Mucin has been described in the fluid, but if present the amount is very small.

Pus (see "Inflammation," Vol. I.).

Cerebrospinal fluid (see "Pathology of Nervous System," Vol. VII.).

Cytology.—The examination of the cells contained in effusions has within recent years assumed some importance as an aid to diagnosis. It is generally recognised that cytodiagnosis should be regarded as a valuable link in the chain of evidence, but it is unsafe to rely exclusively upon it. In connexion with the examination of cerebrospinal fluid (see Vol. VII.) it has risen into considerable prominence. In the case of pleural effusions it has been established that predominance of lymphocytes points to tuberculosis, of polymorphonuclear leucocytes to inflammation, and of endothelial cells to mechanical transudation (see article "Pleurisy"). The same general truth holds also in regard to effusions into the peritoneum, but the presence of disturbing factors appears to be more frequent in this serous sac. The following summary of a few important investigations on this subject relates mainly to the peritoneal fluid. The technique employed is admirably given in a recent paper by E. A. Ross. Tuffier and Milian approached the subject from the point of view of distinguishing between tuberculous peritonitis and ovarian cysts ; and they appear to be the first who definitely discovered the great preponderance of lymphocytes and mononuclear cells in the fluid in the first-named of the two diseases. They give the percentage of these cells as 78. In the fluid of ovarian cysts, there are, on the contrary, large numbers of cells five times larger than leucocytes, round or oval in shape, and filled with vacuoles : columnar ciliated cells are also present. Their statements regarding the fluid of tuberculous disease was confirmed by Dopter and Tanton, and by many subsequent observers. Gilbert and Villaret worked mainly with ascitic fluids produced by hepatic cirrhosis, and pointed out that though in the main endothelial plates are the most abundant of the cells present, yet in later stages, and

especially if infection or tuberculous complications set in, the number of polynuclear cells and lymphocytes may be very considerable. Cade's paper, which was published in the same year, gives a very complete bibliography of the subject, and deals with a large number of peritoneal fluids in a very systematic way. The following are the averages of the percentage numbers of the three principal kinds of cells present:—

Ascites due to	Endothelial Cells.	Lymphocytes and Mononuclear Cells.	Polynuclear Cells.
1. Mechanical causes (e.g. cirrhosis) . . .	69	22	9
2. Tuberculosis . . .	10	71	19

In other cases of mixed origin, the cytology is very variable. In effusions which accompany neoplasms, it also appears difficult to state any general rule. Cade describes in such cases a very frequent excess of endothelial cells often massed together, a number of small vacuolated cells of irregular form, and often with two nuclei, together with a variable proportion of lymphocytes and polynuclear leucocytes. In carcinoma Dock states that more cells are seen exhibiting mitotic changes than are found in ascitic fluid of non-malignant origin, and the mitosis in some cases is atypical; and Gilbert and Villaret describe in the cases of cancer they examined an excess of polynuclear cells, associated with smaller cells of variable contour exhibiting more or less degenerative change.

In the face of so much discrepancy, most observers will probably agree with Ross when he concludes that cytodiagnosis is of little value in dealing with malignant disease. Ross concurs with the other observers quoted in reference to the character of the cells in mechanical effusion and in tuberculosis, and he also has found that acute inflammation produced by other pyrogenetic organisms is accompanied by the almost exclusive presence of finely granular polynuclear corpuscles.

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DISEASES OF THE KIDNEY

GENERAL PATHOLOGY OF THE RENAL FUNCTIONS.

NEPHRITIS.

NEPHROPTOSIS.

OTHER DISEASES OF THE KIDNEY—

ABNORMALITIES ; METHODS OF EXAMINATION ; ANEURYSM OF RENAL ARTERY ; PERINEPHRIC EXTRAVASATIONS ; PERINEPHRITIS AND PERINEPHRIC

OTHER DISEASES OF THE KIDNEY— *continued*

ABSCESS ; TRAUMATIC NEPHRITIS ; ABSCESS ; FISTULAS ; URINARY FEVER ; HYDRO-NEPHROSIS ; TUBERCULOSIS ; ACTINOMYCOSIS ; SYPHILIS ; CALCULI ; CALCULOUS ANURIA ; NEW GROWTHS.

MALFORMATIONS AND DISEASES OF THE URETER.

GENERAL PATHOLOGY OF THE RENAL FUNCTIONS

By Prof. J. ROSE BRADFORD, M.D., F.R.S.

A. THE URINE

In health the composition of the urine remains fairly constant, with some fluctuation in the amounts of the individual constituents. In disease the changes in its composition are due either to morbid processes in the kidney itself interfering with its excretory functions, or to changes in the general tissue metabolism producing substances not normally found in the economy; and these, after circulating in the blood, are excreted in the urine. Not infrequently the excretion of these bodies in the urine may injure the kidneys. Disease may alter the quantities of normal constituents of the urine, or it may lead to the presence in it of abnormal substance.

Urinary Water.—The quantity of water voided by a healthy adult in twenty-four hours is from 40 to 50 ounces. These limits may be exceeded or not reached; the quantity may rise to 80 or fall to 20 ounces. In health, inasmuch as the water in the tissues remains fairly constant, the quantity of the urine is affected by (i.) the amount of fluid consumed; (ii.) the amount of fluid eliminated by other channels, as by the lungs, skin, and alimentary canal.

In disease the amount of water in the tissues may undergo great variations, and these variations will produce effects on the urinary flow; thus dropsy, from whatever cause, will necessarily lead to a diminution in the quantity of urine. Ultimately the amount of urine is determined in health by the functional activity of the glomerular tuft, and this in turn depends upon (a) the activity of the glomerular epithelium; (b) the rate of the flow of the blood through the tuft. Besides these two factors it is possible that the nervous system may control the kidney, so as to influence the amount of urine, and even to cause suppression. Further, recent work has shewn that the secretion of urine may be influenced by chemical products derived from ductless glands. Thus, the pituitary gland elaborates a substance having a powerful diuretic action (Schäfer and Herring), hence an inter-relation between the activities of different glands may be affected by chemical as well as by nervous agencies.

The varying blood-flow through the kidney is, however, the factor about which most is known. Dilatation of the renal vessels, produced either through the nervous system, or on the direct stimulation of the blood-vessels by some chemical constituent of the blood circulating through the organ, causes a greatly increased flow of urine. The diuresis produced by local dilatation of the renal vessels is still further increased if the local renal dilatation is accompanied by a general constriction in other vascular areas. Conversely, local constriction of the renal vessels and general dilatation of all the other vessels of the body, by lessening the blood-flow through the kidney, cause a diminished flow of urine. Substances that produce an increased flow of urine—for instance, urea, sugar, caffeine, and so forth—cause experimentally a dilatation of the renal vessels; but not always a simple dilatation: thus, caffeine produces an initial constriction followed by dilatation. Drugs like digitalis cause an increased flow of urine, although they produce constriction of the renal vessels; but here the result is due to the considerable rise in general blood-pressure and the increased velocity of the blood whereby, notwithstanding the constriction of the renal vessels, more blood probably flows through the kidney in a given time. The action of substances like urea, which cause diuresis with vascular dilatation, is a local one on the kidney, since all the effects can be produced after complete division of the renal nerves.

Although the state of the renal vessels is the factor in the excretion of urine with which we are best acquainted, my experiments shew that the quantity of kidney substance has a profound effect on the amount of urine excreted. The removal of small portions either from one or both kidneys is followed by an increase in the quantity of urine secreted; and if so much as two-thirds of the total kidney weight be removed, the urinary flow may be permanently doubled without undergoing any other alteration in its composition. If a considerable wedge be removed from each kidney a still greater increase of the urinary water is obtained. The removal of three-fourths of the total kidney weight is followed, not only by a still greater increase in the urinary flow—so that it may be quadrupled in amount—but also by an augmentation of the excretion of urea. These observations shew that the removal of portions of the kidney influence the amount of urinary water excreted very materially; and this notwithstanding the fact that the remnants of kidney do not undergo any marked pathological change.

Although no nerves have been found that exercise any influence on the secretion apart from the vasomotor mechanism, yet no doubt the secretion of urine may sometimes be totally arrested without any great effect being produced on the renal circulation at the same time. To expose the ureter and put a cannula into it will sometimes completely arrest the excretion of urine. On the other hand, puncture of the medulla causes a great increase in the amount of urine; and although the effects of the latter experiment may be explained as a result of vaso-motorial influence, this cannot be the case in the former, since there is no

experimental evidence that interference with the ureter leads to any circulatory changes in the kidney.

In disease the quantity of the urine may be increased or diminished—the latter more usually than the former. If increased, the increase may be either permanent or temporary. In diabetes mellitus and in diabetes insipidus the increase is permanent. In lardaceous disease of the kidney and in renal cirrhosis the increase, although not present throughout the disease, yet persists for considerable periods. In chronic parenchymatous nephritis, or diffuse nephritis, considerable temporary increase is seen during the period of the subsidence of the dropsy, and also subsequently when all trace of dropsy has disappeared. In diabetes mellitus the increased excretion is usually held to be due to the presence in the urine of large quantities of sugar and urea. In diabetes insipidus the cause of the diuresis is obscure, but it is attributed to some functional bulbar change, causing dilatation of the renal vessels (*vide Vol. III. p. 215*). In both diseases there is great thirst, but this is probably the result rather than the cause of the flow of urine. In certain cases of diabetes insipidus the kidneys are functionally incapable of excreting any but a dilute urine (Mohr), whilst in others they are still able to prepare a urine of fairly high osmotic tension when either the quantity of water available for excretion is reduced or the amount of salts to be excreted is increased. In the one case, therefore, polyuria, in the other polydipsia, would seem to be the primary symptom of the disease (Finkelburg).

In diffuse nephritis the quantity of urine varies inversely as the amount of dropsy. In the other chronic destructive diseases above mentioned the increased flow is due either to the diminution in the amount of kidney substance or to the altered state of the blood-vessels or to the abnormal blood-pressure.

Most diseases lead to a diminution in the quantity of urine; thus febrile disorders, with the increased loss of water by sweating and by hurried respiration, are marked by the excretion of a scanty concentrated urine. Dropsy, whether of cardiac, renal, or hepatic origin, leads to a deficient and scanty excretion of urine. Diseases causing profuse diarrhoea may even cause complete suppression, as in cholera. All diseases producing a diminished flow of blood through the kidney owing to venous congestion—for example, thrombosis of the renal vein or vena cava, cardiac valvular disease, pulmonary lesions, and so forth—lessen the quantity of urine. Lastly, acute and certain chronic inflammatory and other destructive diseases of the kidney diminish the flow. This failure in excretion, however, is more frequently seen in acute and subacute nephritis than in well-established chronic nephritis.

The diminution in the quantity of urine may go on to absolute suppression, of which two varieties are described, the so-called obstructive and non-obstructive suppressions. In the former there is some direct impediment to the exit of the urine along the ureter; in the latter no such obstruction exists, the renal pelvis and the ureter are quite patent; nevertheless no urine, or only very small quantities of it, are excreted.

The latter condition is much the more serious, and usually ends fatally in from two to four days, or even in twenty-four hours. It is seen in very acute nephritis, sometimes also in chronic nephritis, and in certain forms of granular kidney and other diseases of the kidney. It may also be seen during the course of acute specific fevers, as, for instance, in diphtheria, without any marked alteration in the kidney; also in perforative peritonitis, and after severe injuries. In these latter cases it may occur with kidneys apparently perfectly healthy and not presenting any coarse lesions post-mortem. This form of suppression has been known to occur after operations on the kidney, when one organ has been exposed and incised with the view to the detection of a stone, and yet where no stone or other disease has been found. In many of these cases the kidneys are not healthy; but in some cases total suppression has followed exploratory incision into the kidney, and yet post-mortem examination has revealed no obvious disease of the kidneys. In rare instances thrombosis of the renal arteries leading to necrosis of the renal cortex occurs in the puerperal state; this affection is bilateral, and consequently may lead to the production of complete suppression.

Suppression is not an uncommon sequel of catheterisation, when the kidneys are diseased secondarily to mischief in the lower urinary tract.

Obstructive suppression is seen in bilateral calculous disease, and where after one kidney has been practically destroyed by calculous pyelitis the ureter of the only active kidney becomes blocked by stone. It is also seen where, owing to disease in the pelvis, as in carcinoma of the uterus, both ureters are simultaneously closed. In these conditions the first effect is not suppression, but rather the production of hydronephrosis; no urine is emitted, but it is still secreted by the kidney. Sooner or later, however, if this condition be not relieved actual suppression ensues (*vide* p. 702).

Specific Gravity.—The specific gravity of the urine is usually from 1015 to 1025, but it may fall as low as 1002 persistently, as in diabetes insipidus, or it may rise as high as 1060. Persistently low specific gravity, especially in the urine voided in the early morning, or in the urine of the total twenty-four hours, is produced by such diseases as diabetes insipidus, cirrhosis of the kidney, lardaceous disease of the kidney, chronic diffuse nephritis, hydronephrosis, cystic kidneys. Severe Bright's disease, however, sometimes even fatal Bright's disease, can exist with a urine having a specific gravity as high as 1025.

It must not be forgotten that the specific gravity of water, taken as 1000 at 4° C., falls when the fluid is warmed. It is 999 at 15° C., 997 at 25° C., 994 at 35° C., and 992 at 40° C. Hence, unless the proper allowance is made, very misleading results may be obtained if the specific gravity of a specimen of urine be taken before it has cooled down to the ordinary temperature.

The specific gravity is raised by the presence of large quantities of urea and salts in the urine, and by sugar. A character of the presence of the last substance, however, is a high specific gravity of a pale, dilute-

looking urine ; thus, a specific gravity of 1035 in pale urine suggests sugar, but a specific gravity of 1035 in a high-coloured febrile urine would have no such significance. Sugar may, however, be present, even in a considerable quantity, with a specific gravity as low as 1010 ; and when the specific gravity is raised by the presence of sugar the two do not necessarily vary together. A higher percentage of sugar may be present with a rather lower specific gravity. This is due to the effect on the specific gravity of other constituents, and more especially of urea and salts. In diabetes, provided the flow of urine be large and hence dilute, the specific gravity gives a fairly accurate notion of the quantity of sugar ; but this is not the case if the quantity of urine be comparatively small.

Cryoscopy and Electrical Conductivity.—These two methods, borrowed from physical chemistry, enable measurements to be taken of the number of dissolved molecules (that is to say, the molecular concentration) and the number of ions in specimens of urine. In cryoscopy the depression of the freezing-point of urine is measured in some form of Beckmann's apparatus, and it has been found that in the mixed urine of twenty-four hours from healthy persons the freezing-point varies between -0.87° and -2.43° , whilst the examination of individual samples naturally shews still greater variations. Koranyi found the average freezing-point to be -1.7° C. in health. As albumin has very little effect upon the freezing-point, cryoscopy may give useful information as to the amount of salts and extractives present in an albuminous urine that is not afforded by determination of the specific gravity ; in other cases, the great hopes that were aroused by its introduction in 1897 have not been realised. The electrical conductivity of a urine may be measured by the use of a Kohlrausch's apparatus, and gives an indication of the quantity of free ions and the inorganic salts present, being unaffected by the presence of non-electrolytes like sugar or albumin. It was hoped that these two methods would enable comparisons to be made between the functional activities of the two kidneys respectively. Unfortunately, the two kidneys may shew large differences in the quantity and composition of the urine they secrete during identical periods in health, and up to the present time neither cryoscopy nor estimation of the electrical conductivity of urine have proved useful in diagnosis.

Reaction.—The reaction of the normal urine is acid, but the acidity varies largely under the influence of meals. Although the urine voided in health is usually acid, the urine secreted by the kidney undergoes great fluctuations in reaction. Thus, the morning urine is highly acid ; the urine secreted two to three hours after a meal may be even alkaline, but probably, owing to admixture with acid urine in the bladder, the fluid voided will still be acid. The reaction of the normal urine is most influenced by diet ; and, speaking broadly, an animal diet increases the acidity and a vegetable diet diminishes or even annuls this reaction. The acidity of the total urine in twenty-four hours in health is equivalent to from 1.5 to 2.3 grams of hydrochloric acid, and is dependent upon the

presence of acid phosphate of sodium. Probably as meat contains a considerable amount of this acid phosphate it is this constituent of meat which increases the acidity of the urine.

If in disease the quantity of urine be diminished, as in fever, the relative acidity is increased.

Patients living "high" and suffering from so-called lithaemia also excrete highly acid urine. The urine in diabetes, more especially in diabetic coma, the so-called acetonaemia, is highly acid, and may contain a considerable quantity of abnormal acids, more especially β -oxybutyric acid and its derivative diacetic acid.

In disease the acidity of the urine is more frequently diminished, and not uncommonly it is alkaline. The acidity is greatly diminished in cases of dilated stomach, and especially, it is said, as the result of washing out the stomach. The acidity of the urine cannot be increased beyond a certain point by the addition of acids to the diet, for when the supply of alkaline carbonates at the disposal of the organism for the neutralisation of such acids runs short, ammonia is formed in increased quantity in the catabolism of the proteins in the body, and is used up in neutralising the excess of acid ingested. The herbivora possess no such protective mechanism, and consequently stand feeding with acid food ill.

Two varieties of alkaline urine are recognised—one in which the alkalinity is dependent upon the presence of a fixed alkali, and the other in which it is dependent on the presence of a volatile alkali. The former is often associated with a diet rich in vegetable matter, and it is sometimes seen for long periods in nervous, dyspeptic, neurasthenic, hypochondriacal patients. Such urine is frequently milky from the precipitation of phosphates, more especially calcic phosphates. It is not a condition of any very great consequence, except that it may possibly lead to the precipitation of amorphous tricalcic and also of monocalcic phosphates, and may cause the formation of some of the rarer phosphatic stones.

Alkalinity from volatile alkali, on the other hand, is a very serious condition, and is usually dependent on decomposition of the urea into carbonate of ammonia, owing to microbic infection of the urine, usually from the introduction of dirty catheters. Sometimes the infection reaches the urine from within, owing to the rupture of an abscess into some part of the urinary tract; and it is probable that occasionally organisms may reach the urinary bladder, either by ascending the ureter or even by passing through the kidney from the blood. Alkaline urine loaded with bacteria is occasionally seen in Bright's disease, but a high degree of bacilluria may exist without any change in the kidney.

Normal Pigments.—Attempts have been made to explain the colour of the normal urine as dependent upon a single pigment, but at the present time there can be no doubt that several pigments are present, and, further, that the yellow colour is not dependent upon any substance yielding a banded spectrum. Normal fresh urines, when examined spectro-photometrically, shew relative as well as absolute variations in the extension coefficient for any part of the spectrum. In this respect

opinion has reverted somewhat to the earlier views of Schunk and Thudichum. The following pigments have been obtained from normal urine :—

Urobilin, a pigment obtained from the urine by precipitation with lead salts and subsequent extraction with alcohol acidified with sulphuric acid; or by saturation of the urine with ammonium sulphate. Urobilin is readily soluble in chloroform, and yields a definite absorption band at F.

Some observers think that the yellow colour of the urine is dependent upon this body ; others that, although it is undoubtedly present in normal urine, yet, as only traces are present, it plays an unimportant part in the production of the normal colour. The main points in support of this latter view are that, whereas urobilin itself is freely soluble in chloroform, chloroform does not take up the yellow colour of normal urine ; and that, whereas urobilin yields a very definite and dark absorption band at F, normal urine, even when viewed in deep layers, only shews a shading here. To account for the small amount present normally, and also for the fact that this amount is increased by exposure, oxidation, and the like, it has been assumed that a mother substance, or chromogen of urobilin, is present in normal urine, which yields urobilin on oxidation. Urobilin is present in the bile, and is probably not identical (Garrod and Hopkins) with hydrobilirubin, formed from bilirubin by the action of potash and sodium amalgam. It is identical with the body formed from acid-haematin by the action of zinc and hydrochloric acid and with the faecal pigment stercobilin.

Uroerythrin.—This is the pigment that causes the pink colour of the uratic deposits, seen occasionally even in health. This pigment can be extracted from normal urine by means of amyl alcohol. It is an amorphous reddish substance, acid in reaction, soluble in alcohol, ether, and water. The alcoholic extract of pink urates yields two absorption bands between D and F. Uroerythrin, treated with caustic alkalis, yields a green colour.

Haematoporphyrin has been found in the urine as a result of the administration of sulphonal, nearly always in women, and occasionally after trional and tetronal. It also occurs in other conditions, and intermittent haematoporphyrinuria has been observed (Garrod, Monro). It is present in minute traces in normal urine, is the outcome of perverted catabolism of haemoglobin and not of excessive haemolysis, and cannot be regarded as a symptom of any special disease. The colour of urines containing haematoporphyrin is not entirely due to that body (Garrod). Urohaematoporphyrin was described by MacMunn as a pigment present in the urine in certain diseases ; but it is really a mixture of haemato-porphyrin and urobilin.

Urochrome.—None of the above-mentioned pigments, although present in normal urine, will account for the yellow colour of the fluid, and to a substance yielding a yellow solution, but not yielding any bands spectroscopically, Thudichum gave the name of urochrome ; this observation has been revived and extended by Dr. Garrod. Thudichum

obtained a substance forming yellow crusts, freely soluble in water, fairly so in ether, less in alcohol. Schunk found two yellow pigments, one soluble in ether, the other not. Dr. Garrod has obtained an amorphous brown substance, insoluble in ether and chloroform, freely soluble in water. Although there are differences in solubility between the results of these various observers, there can be no doubt that they all operated on the same substance, and that this yellow pigment does not yield a banded spectrum; moreover, by Garrod's method at any rate, the urine was not acted upon by powerful reagents, capable of causing decomposition of the pigments present. Hence urochrome is probably the substance to which urine owes its colour.

Humous Pigments.—Normal urines are found to darken materially when treated with mineral acids, and amongst the various pigments that are formed under these circumstances the so-called humous pigments described by von Udránszky must perhaps be included. These are dark brown pigments, formed when carbohydrates are treated with acids or alkalis. They yield no bands, and they are soluble in amyl alcohol and in caustic alkalis; inasmuch as the normal urine contains carbohydrate derivatives it is quite possible for these substances to be formed.

The urine, in addition to the pigments described above, contains several other substances which, although not coloured themselves, yield well-marked and characteristic pigments on treatment with acids. The most important of these are the indoxyl and skatoxyl sulphates of potassium.

Indican.—Indigo, more properly termed indigo-blue, does not appear as such in normal urine, but in exceptional cases it may be seen in decomposed urine in quantity sufficient to give the liquid a blue colour. Its urinary precursor is indican, or indoxyl sulphate of potassium, a salt crystallising in colourless shining plates, and derived from the indole occurring normally in the faeces. Mineral acids decompose indican into sulphuric acid and indoxyl, and if air or oxidising agents are absent the indoxyl is transformed into indigo-red. In the presence of air or oxygen it is transformed into indigo-blue. Hence indigo-blue can be made from urine containing indican by adding an equal volume of strong hydrochloric acid, and adding as oxidising agent solution of calcium hypochlorite (Jaffé) drop by drop, avoiding any excess. The Jaffé-Obermayer test for indican is performed as follows. The urine is weakly acidified with acetic acid, precipitated by the addition of one-tenth of its volume of saturated lead acetate solution, and filtered. To 20 c.c. of the filtrate are added 2-3 c.c. of chloroform, and 20 c.c. of pure concentrated (sp. gr. 1.19) hydrochloric acid containing 2-4 grams of ferric chloride (as oxidising agent) in the litre. The mixture is then shaken, and the chloroform is coloured more or less deeply blue by any indigo-blue that may be formed. Indoxyl may also be excreted as indoxyl-glycuronic acid, to the extent of 5-20 mgrms. daily (Jaffé).

Skatole Pigments.—These have a similar origin to the indole pigments;

part of the skatole formed in the intestine yields potassic skatoxyl sulphate, and is excreted in the urine. It is also normally excreted in the urine combined with glycuronic acid. On treating urine containing this body in abundance with an acid, the fluid becomes of a deep red colour. This pigment, like indigo, is present in increased amounts in the urine in constipation ; and this perhaps accounts for its presence in diabetes and in chlorosis. Its chemical composition is unknown, and Rosin has thrown doubt upon its existence.

Abnormal Pigments.—In disease, normal pigments may be excreted in greatly increased quantity ; or again pigments, not normally present, may be excreted. Amongst the latter, haemoglobin and its derivatives and bile pigments may be mentioned.

Urobilin.—As stated above, the normal urine contains small amounts of urobilin—from 30 to 140 mgrms. per day in health (Saillet, Hoppe-Seyler) ; but in a great number of diseases urine is voided of a reddish-brown colour and containing a large quantity of this pigment. To the eye the urine looks as if it contained bile or altered blood pigment ; in fact, this mistake is often made, more especially because such patients are often distinctly yellow, and the conjunctivæ are yellow. The stools, however, are of normal colour, and in testing the urine no bile reaction is obtained ; on spectroscopic examination the deep black absorptive band at F, characteristic of urobilin, is seen. Some observers consider that this urobilin is different from the urobilin in normal urine, and that it only exists in the urine normally as a chromogen ; to it the name of pathological or febrile urobilin has been given. There is considerable doubt, however, whether there is any distinction between the so-called normal and so-called pathological urobilin, and I have therefore used the name urobilinuria, as I believe that the substance is the same as the so-called normal urobilin, but that it is present in greatly increased amount. The important point is that in disease this pigment may be found in the urine in such quantity as to cause a superficial resemblance to bile-stained urine.

Urobilin is formed in the intestines by the action of bacteria on bilirubin and is the same as stercobilin ; it may also be due to excessive haemolysis and extravasations of blood. In pernicious anaemia it is this pigment that causes the well-known brown colour of the urine. In many of the conditions in which urobilin is excreted in quantity in the urine the patient's skin and mucous membranes are yellow, and at one time this was regarded as due to the presence of urobilin as such in the blood and tissues (*vide Urobilin Jaundice*, p. 84). The blood of these cases has, however, been shewn to contain bile pigment, although there is none in the urine (acholuric jaundice). Urobilin is also found in the urine in increased amount in cirrhosis of the liver, with or without the presence of jaundice and of bile pigments in the urine. In febrile diseases the dark colour of the urine is due in part to excess of urobilin ; and in paroxysmal haemoglobinuria urobilin, in addition to haemoglobin derivatives, has been found in the urine.

Haematuria. — Here blood-corpuses are present in the urine in varying amount. Blood may be added to the urine for purposes of deception ; otherwise haematuria is due to haemorrhage into some part of the urinary tract. Haemorrhage from the kidney may come either from the kidney substance or from the renal pelvis. The former is seen in acute nephritis and in infarction of the kidney, passive congestion, or tumours ; the latter in pyelitis, in calculous and tuberculous disease. Profuse haemorrhage is sometimes seen in cases of purpura haemorrhagica ; probably it comes from the vessels in the loose cellular tissue of the renal pelvis, as in fatal cases copious submucous haemorrhages are seen in this situation. In granular contracted kidney very profuse haemorrhage is sometimes seen, so that the urine is bright red in colour ; and here also it is probable that the haemorrhage is really from the renal pelvis and not from the kidney itself. In cases in which the haemorrhage is actually from the kidney substance the urine will contain renal casts and very probably blood casts. When the blood comes from the kidney or pelvis of the kidney, the blood is intimately mixed with the urine ; and if it is present in small quantities only, the urine will be smoky from the action of the acid salts of the urine on the blood pigment, some of the haemoglobin being converted into acid-haematin and methaemoglobin. If the blood is present in large quantities it will impart a bright red colour to the urine, notwithstanding its renal origin.

In very profuse haemorrhage from the kidney and from the renal pelvis clots may form and temporarily block the ureter, and the patient may suffer from attacks of renal colic. Casts of the ureter may sometimes be passed.

The bladder is a common source of blood in the urine, and vesical haemorrhage may be so profuse that the organ may become distended with blood-clots. In vesical haemorrhage the blood may be uniformly mixed with the urine, but very frequently the blood is only seen, or is seen more abundantly in the last portions of urine passed, the first portions being quite clear. In prostatic haemorrhage the bleeding is also apt to be seen at the end of micturition. Haematin is often found in the urine in cases of vesical bleeding, the blood having been decomposed by the acid urine.

A small amount of blood in the urine associated with a large amount of albumin points to the existence of renal disease. The blood in the urine may, by the eye, be confounded with bile and with urobilin. From the former it may be distinguished at once by the greenish tinge always seen on the surface of urine containing bile. From urobilinuria the mistake may be avoided at once by spectroscopic examination. Blood is most readily detected by microscopic examination of the lower strata of the urine after settling or centrifuging. The blood-corpuses may be seen either but little altered or crenated ; occasionally in dilute urine they may be distended and difficult to recognise as blood-corpuses. As confirmatory tests the guaiacum test, Heller's test, and the spectroscope may be used ; but the last is not of much avail when traces of blood only

are present. Haemin crystals may also be formed, and afford a very certain indication of the presence of blood.

Haemoglobinuria.—Here the colouring matter only of the blood, more or less altered, is found in the urine. It is exceptional for haemoglobin to be present alone; it is usually mixed with methaemoglobin. The redder the urine, the greater the amount of haemoglobin; the browner, the more methaemoglobin. It is possible that in many cases haematin is also present. Haemoglobinuria is seen under the following conditions:—

(a) *Paroxysmal haemoglobinuria* or *haemoglobinuria a frigore*. In sufferers from this disease exposure to cold is followed by the disappearance from the circulation of very large numbers of blood-corpuscles; thus, in an attack the patient may lose half the total number of blood-corpuscles; the urine is as dark-coloured as porter, and contains no blood-corpuscles, but a granular debris and oxalates. It is loaded with albumin, and the brown colour is due to a mixture of methaemoglobin, haemoglobin, and urobilin. As the attack passes off the urine becomes of a lighter and redder tint, and finally returns to its normal colour.

Dr. Eason and others have shewn that the blood-serum of these patients contains a haemolysin, and that under the influence of cold this haemolysin combines with the red corpuscles and leads to the liberation of the haemoglobin. Paroxysmal haemoglobinuria has been observed after muscular exertion, and in one instance after recurrent haemorrhages of traumatic origin; in this case it was suggested that an auto-haemolysin was produced (Barrett and Ensor).

(b) *So-called symptomatic haemoglobinuria.* This is a condition in which the haemoglobinuria is simply an accompaniment of another malady. Thus, it is seen in black-water fever and occasionally in Raynaud's disease, and the phenomena are much the same as in the idiopathic haemoglobinuria. It also occurs after severe burns and in acute infective diseases.

(c) *Toxic haemoglobinuria.* This may be produced in poisoning by arseniuretted hydrogen, chlorate of potassium, pyrogallic acid, naphthol, or carbolic acid.

Haemoglobinuria is most certainly recognised by spectroscopic examination; the bands of the methaemoglobin resemble those of oxyhaemoglobin, and, moreover, the band in the red is very characteristic of methaemoglobin. If the amount of haemoglobin be large, and the urine be examined without dilution, only the band in the red will be seen, all the rest of the spectrum being cut off; but on dilution the two bands in the yellow will be seen, and care must be taken not to dilute too rapidly, otherwise the band in the red will be missed. Heller's test is also applicable. On microscopic examination of the urine, either no blood-corpuscles or extremely few are seen. A number of droplets of a yellowish colour are frequently found. In fatal cases these are also seen in the cortical tubules of the kidney.

Melanin, a pigment containing sulphur, is rarely found in the urine

of patients with melanotic sarcoma invading the viscera, especially the liver. Usually the pigment is passed in a colourless form—melanogen—and the urine darkens gradually on exposure to the air, or on the addition of any oxidising agent (Eiselt's reaction). Thus on the addition of nitric acid to such urine it becomes black in colour, the chromogen of melanin being converted into melanin. Ferric chloride, when added to such urines, causes a greyish-brown or black precipitate, soluble in excess of ferric chloride. Bromine water, when added to the urine, gives a yellow precipitate, which gradually blackens. In rare instances the urine may have a *café-au-lait* colour when passed.

Choluria.—In jaundice the bile pigments are found in varying quantity in the urine, and impart to it a colour varying from reddish-brown to almost black. The upper surface of the urine, on an oblique illumination, has a greenish tinge, and on shaking such urine a greenish-yellow froth is seen. Bile pigments can often be recognised in the urine in cases of jaundice before jaundice appears, and the yellow colour of the skin may persist at a time when the pigmentation of the urine is slight or absent. In acid urines crystals of bilirubin may be precipitated. Although bile pigments are present in the urine in obstructive jaundice, and are readily recognised, this does not apply to bile salts; and even in cases of complete and permanent obstruction of the bile-ducts it is difficult to detect them in the urine unless special methods are employed. For the recognition of bile pigments Gmelin's nitric acid test is the best; but the acid should not contain too much yellow fuming acid, as with this the oxidation occurs too rapidly, and the play of colours is not readily seen. The test can be performed on a plate or blotting-paper or on a slab of plaster-of-Paris. These methods are all better than pouring the urine on the nitric acid in the bottom of a test-tube. Bile cannot be said to be present unless a green colour is seen as the first colour in the play. Bile pigments may be precipitated with milk of lime, the precipitate collected and treated with water, and then shaken with chloroform acidified with acetic acid. The chloroform solution of the bile pigments may then be used for Gmelin's reaction. Troussseau's test, namely, the addition of dilute tincture of iodine to urine with the production of emerald green colour if bile pigment be present, is a convenient clinical test and is more delicate than Gmelin's. The recognition of the bile salts in the urine is more a matter of scientific than of clinical interest [*vide* "Functions and Functional Disease of the Liver"]. Occasionally their presence may be recognised by Pettenkofer's reaction in the urine itself, that is, by treating the urine with a solution of sugar and some sulphuric acid, and shaking; the purple colour characteristic of the reaction may be seen in the froth. More usually this procedure fails, and then some ounces of urine must be evaporated to dryness, the residue extracted with alcohol, the salts precipitated by ether, dissolved in water, and Pettenkofer's reaction sought with this solution. Since the presence of bile acids lowers the surface tension of urine, tests have been based on this. In Hay's test finely powdered sulphur is sprinkled on the

surface of the urine ; if it sinks, bile acids are present. To the eye, urine containing bile may be confounded with urine containing large quantities of urobilin, and with urine containing decomposition products of haemoglobin, such as methaemoglobin and haematin.

It is of interest to note that in cases of external biliary fistula, with complete obstruction of the bile-ducts, the urine maintains its normal yellow colour, notwithstanding that all the bile secreted is passed outwards, and none enters the intestine. This throws considerable doubt on the view that the urinary pigments (urochrome, urobilin, etc.) are derived ultimately from the bile pigments.

Pyrocatechin and hydroquinone.—The former substance occurs normally in small amounts in the urine, and is greatly increased in cases of carboluria. The latter occurs only in cases of poisoning with carbolic acid. Both these substances exist in the urine as ethereal compounds of sulphuric acid. Urine containing pyrocatechin is colourless when passed, but darkens on exposure to the air ; if this substance be abundant, the urine will become black. It is to this body and to hydroquinone that the greenish-black colour of the urine in carboluria is due.

Alkaptonuria.—In certain rare instances urines, although of a normal colour when passed, acquire a deep brown, and ultimately a black colour on exposure to air. The addition of alkalis causes the brown colour to become much darker, and, further, these urines reduce Fehling's solution, although no sugar is present. In not a few instances the error of attributing the reduction to sugar has been made, but this can always be avoided by performing the fermentation test which is negative in alkaptonuria. In many instances the condition has first attracted notice in infancy, owing to the staining of the linen by the urine. According to Dr. Garrod the condition is more common in males than in females, and in the great majority of cases the anomaly dates from birth or early childhood. In some instances life-long alkaptonuria occurs in several members of a family, but it is not hereditary ; in its incidence it shews a striking resemblance to albinism. Alkaptonuria causes no discomfort or symptoms of any kind, and may be regarded as a chemical malformation or freak of metabolism. In a few rare instances temporary alkaptonuria has been found in association with gastro-enteritis, gastric ulcer, pulmonary tuberculosis, tuberculous peritonitis, and diabetes. The rare affection ochronosis, in which blackening of the cartilages is a characteristic feature, is sometimes accompanied by the excretion of a urine that darkens on exposure ; and although in some cases the urine has not reduced Fehling's solution, and so alkaptonuria was not really present, in others the patients were known to be alkaptonurics prior to the development of the ochronosis.

Homogentisic acid (hydroquinone-acetic acid), an aromatic acid, is present in the urine in all cases of alkaptonuria, and it has been stated that uroleucic (hydroquinone- α -lactic) acid is also present in some cases, but the evidence for this seems insufficient (Garrod and Hurtley). The administration of tyrosine to the alkaptonuric greatly increases the

excretion of homogentisic acid, although it fails to do so in the normal individual. Tyrosine, a product of the disintegration of protein, is the parent substance from which the homogentisic acid is derived, and alkaptonuria would appear to be the result of some abnormal protein metabolism, the details of which are at present unknown; but possibly the condition is really due to some peculiar intestinal decomposition (*vide Vol. I. p. 548.*)

Nitrogenous Extractives.—About 15 grams of nitrogen are excreted daily on an average during health, and the most important nitrogenous constituents of the urine are urea, uric acid and creatinine; others, such as xanthine, guanine, hippuric acid, although present, are not of great clinical importance.

Urea.—Normal human urine contains, roughly speaking, 2 per cent of urea, occasionally rising in health to as much as 3 per cent. The daily quantity excreted has been stated to vary between 22 and 40 grams, the average being usually stated at some 30 grams. Approximately 0·5 grm. of urea is excreted per kilogram of body weight per day. Children excrete rather more relatively to their body weight. Normally the amount of urea excreted is largely dependent on the diet, and hence is greatly increased after meals. Copious water-drinking increases the urea excretion, at any rate temporarily. Exercise does not lead to any notable increase. In disease the excretion may be diminished or increased, and if increased, the increase may be absolute or relative, temporary or permanent.

Observations on the urea excretion in disease are of little value unless the amount and nature of the foods consumed be taken into consideration. In diabetes mellitus the quantity of urea excreted is greatly and permanently increased, and here the increase is dependent largely upon the increased appetite and nitrogenous diet, partly also upon the wasting.

In diabetes insipidus the quantity of urea is also slightly increased. In febrile diseases the percentage of urea is greatly increased, owing to the density of the urine; and the amount is always relatively increased, since even if quantities of urea, equal to the normal, are excreted, owing to the failure of appetite the amount is really greater than that excreted by a patient with a normal temperature on the same diet.

In wasting diseases, such as cancer of the oesophagus and stomach, associated with vomiting and with practical starvation, the amount of urea is diminished; and this is the case also in diseases destroying the liver substances, as in portal cirrhosis; it reaches its minimum in acute yellow atrophy, in which the urea may entirely disappear from the urine. In renal diseases the urea is diminished in cases of consecutive nephritis, in which urine of a very low specific gravity is passed, containing a very small percentage of urea. In acute nephritis also very little urea is passed, owing largely to the great diminution in the quantity of urine.

In chronic nephritis the amount of the urea excretion varies. In

cases associated with dropsy, and where, therefore, but little urine is secreted, the quantity of urea excreted is small in amount; but in cases of chronic nephritis not accompanied with dropsy, and where there is no uræmia, the quantities excreted are often equal to those seen in health; and in my experience I have found it is not uncommon for daily quantities of 30 grams to be passed. It is usually held that in chronic nephritis a sudden and great diminution in the urine and urea excretion points to the imminence of uræmia.

In renal fibrosis considerable quantities of urea may be passed, and it is not uncommon, in cases of this disease, for uræmia to occur at a time when the patient is passing large quantities of urea, quantities quite commensurate with the amount of nitrogenous food taken, although perhaps the amount is less than that passed by a healthy adult on full diet, such patients being usually on a low diet.

The quantity of urea is usually estimated for clinical purposes by the hypobromite method. This method, even when most carefully performed, gives erroneous results to the extent of 8 per cent. In performing a determination it is important that the hypobromite of sodium should be freshly prepared, that it should not be used in large excess, and that the mixing of the urine and the hypobromite should be carried out very slowly.

Other methods of estimation are those known as Liebig's, the precipitation with phosphotungstic acid, and the Mörner-Sjöqvist-Folin method. These methods, however, are not commonly employed in clinical work.

Uric Acid.—This substance is excreted in amounts varying from 0·2 to 1·4 grams a day. It is probably present in the urine in the form of a quadriurate, but much doubt has been thrown on the existence of quadriurates as definite compounds. Uric acid is not present in the urine as such, but some authors think it is present as a biurate kept in solution, thanks to an interaction with the phosphates of the urine. Others regard the so-called quadriurates as consisting of a loose compound of one molecule of sodium biurate with a variable number of molecules of uric acid. Uric acid is probably formed in the liver and spleen. It is known definitely that it is formed in the liver of birds; but in the mammal the seat of its formation is largely a matter of inference, and it has been asserted that it is formed in the kidney. The amount excreted is largely increased by meals, and the increased excretion after meals is said to occur sooner than the increased excretion of urea. The uric acid is partly endogenous or derived from the metabolism of the tissues, and partly exogenous or due to the purine bases of the food. The endogenous uric acid is constant in amount for one and the same individual, but varies within considerable limits in different individuals. The amount of the exogenous uric acid is greatly influenced by diet, and hence is much larger when a nitrogenous diet rich in purine bases is taken (see Vol. III. p. 146).

All urines, if kept from putrefaction, deposit uric acid sooner or
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later ; but if it occurs some twelve hours after the passage of the urine, its deposition has no clinical significance ; if it takes place within this time, and more especially if it occurs within four or six hours or sooner, then it becomes important, inasmuch as it might occur while the urine is in the urinary passages, and so lead to the formation of a renal or of a vesical stone.

Uric acid is very insoluble in cold water (1 in 40,000 at 18° C.), but more soluble in boiling water. Uric acid, in fact, derives most of its clinical importance from its insolubility. In a weak alkaline solution, such as 0·2 per cent of bicarbonate of sodium, it is more soluble, owing to the formation of a quadriurate ; but if this solution be allowed to stand, crystals of biurate of sodium are deposited owing to the decomposition of the quadriurate.

Uric acid itself crystallises in the form of rhombic prisms, but the size and shape of the crystals vary with the relative purity of the liquid from which the crystals are formed ; and the process is greatly modified by the presence of albuminous substances in the solution.

If precipitated by an acid from a solution in bicarbonate of sodium, uric acid crystallises in plates ; from the urine, however, the usual form is lozenge-shaped crystals. The crystals are usually brownish-red in colour, from the taking up by the uric acid of some of the urinary colouring matter, more especially uroerythrin ; and, owing to this peculiarity, uric acid deposits are usually recognised at once by the naked eye.

In disease the uric acid excretion is often diminished before the paroxysm of gout, but during and after the attack the amount excreted is increased. It is also said to be diminished in chlorosis and in most chronic diseases. On the other hand, it is increased in pernicious anaemia, in myeloid leukaemia, in febrile diseases, in malaria, and in certain forms of diabetes mellitus, sometimes called gouty diabetes. In pernicious anaemia and in leukaemia the increase may be very great ; thus, in the former, from two to three times the normal amount may be excreted when the patient is taking very little food ; and in leukaemia the increase may be still greater. The quantity excreted, however, is not so important as the rate of its deposition, since urines containing less than the normal amount of uric acid (for example, the urine of renal fibrosis) may still deposit uric acid ; so that the nature of the urine, its acidity, and the amounts of its salts and pigments are frequently matters of more practical moment than the amount of uric acid present.

The deposition of uric acid, as such, from the urine is influenced mainly by the acidity of the urine, the quantity of salts present, and the amount of pigment. The salts of the urine keep the uric acid in the form of a soluble quadriurate or biurate ; hence dilute urines deficient in salts and colouring matter frequently deposit uric acid, whereas a concentrated highly acid febrile urine, containing a considerably higher percentage of uric acid, will lead to the formation of a deposit of urates.

The most delicate test for uric acid is the well-known murexide test. Uric acid or urates are treated with fuming nitric acid and, when cold,

ammonia added ; a beautiful purple-red colour is thus produced. Potash produced a purplish-blue instead of a purple-red colour.

Quantitative Estimation of Uric Acid.—In certain diseases, gout, pernicious anaemia, leukaemia, etc., it may be advisable to determine the quantity of uric acid present ; for this purpose one of the following methods is usually employed :—

Hopkins's Method.—This method will probably supersede all others ; it is based on the fact that ammonium urate is insoluble in ammonium chloride. To 100 c.c. of the urine about 50 grams of powdered ammonium chloride are added, care being taken that some of the salt remains undissolved. After standing for two hours the precipitate is collected on a filter and washed with a saturated solution of ammonium chloride. The precipitate is washed into a small beaker with hot distilled water, and heated to boiling with an excess of hydrochloric acid. After standing for two hours the uric acid separates and is collected and washed on a filter and dissolved in a weak solution of sodium carbonate. The bulk of the liquid is now made up to 100 c.c., mixed with 20 c.c. of sulphuric acid, and titrated with one-twentieth normal potassium permanganate ; 1 c.c. of this solution is equal to .00375 gram of uric acid.

Folin and Schaffer have modified Hopkins's method as follows : To 300 c.c. of the urine are added 75 c.c. of a solution containing 500 grams of ammonium sulphate, 5 grams of uranium acetate, and 60 c.c. of 10 per cent acetic acid in the litre ; five minutes later the mixture is filtered, and to 125 c.c. of the filtrate (= 100 c.c. urine) are added 5 c.c. of strong ammonia solution. The mixture is filtered twenty-four hours later, and the precipitate is washed on the filter paper with ammonium sulphate solution until the runnings are chlorine-free. The precipitate is then washed out into a flask with 100 c.c. of water, 15 c.c. of concentrated sulphuric acid are added, and the solution is titrated at 60°-63° C. with $\frac{N}{20}$ potassium permanganate solution, 1 c.c. of which corresponds to 3.75 mgrms. of uric acid. A correction of 3 mgrms. of uric acid is added for each 100 c.c. of urine, to allow for the solubility of the ammonium urate.

Urates.—As mentioned above, uric acid is normally excreted in the form of a quadriurate, the bases being sodium, potassium, calcium, and magnesium. In health the quadriurates remain soluble, even when the urine cools ; but if the quantity of urine be diminished, as the result of sweating, for example, then the urates are only soluble in the warm fluid, and in the cool become deposited in the well-known brownish red amorphous form. This in time is decomposed, and, provided the urine is not allowed to decompose, deposits crystalline uric acid. The decomposition of the quadriurate into biurate and uric acid is readily effected by distilled water ; so that in order to collect the quadriurate deposit it must be washed and filtered with alcohol and not with water. Urates are abundant in febrile urines, and more especially towards the end of a febrile illness. They are also increased in dyspepsia and other diseases

of the stomach, and in portal cirrhosis of the liver. Urates are also abundant in the dense high-coloured urines excreted in cases of venous congestion due to diseases of the heart and lungs. Occasionally the urates are present in the urine in a crystalline form, more especially the acid sodium and ammonium urate; the latter especially is apt to form crystals with spiny processes which, in the case of children, may cause considerable irritation in the urinary tract, and even in the urethra; and this may lead to the temporary suppression of urine.

In all dense high-coloured urine the risk of mistaking the reduction of copper produced by urates for the effects of sugar must be kept in mind. As a rule, urates require longer boiling to reduce the copper, and they tend to produce a yellowish-green deposit rather than the brick-red deposit seen with sugar. Reliance should be placed in doubtful cases on the presence of some other sugar test, such as the fermentation test and the phenyl-hydrazine test. Other nitrogenous constituents of the urine, such as xanthine, hypoxanthine, are not of sufficient clinical importance to be considered here.

Creatinine, after urea, is the most abundant nitrogenous constituent of the urine, being present in amount of from 1 to 2 grams daily; but, as its solubility is so great, it is a body of little interest to the clinician; thus, although there is twice as much creatinine excreted as there is uric acid, yet the latter is of far greater importance. The creatinine of the urine is partly endogenous or derived from the tissues, mainly if not entirely (Spriggs) from the creatine of muscles, and partly exogenous or from meat in food. In fever the output of creatinine is increased, but to a much less extent than that of uric acid (Leathes). Creatine, which is not present in normal urine, has been found in considerable quantities in the urine of patients with carcinoma of liver (Mellanby). The main importance of creatinine is that it reduces copper like sugar, and hence, occasionally, its presence in the urine in unusual quantity may be mistaken for traces of sugar. Creatinine and urates between them account for a large part of the reducing action of normal urine. The mistake of confounding creatinine and sugar may be avoided, either by precipitating the creatinine by mercuric chloride, or by testing for sugar by the fermentation test.

Leucine and Tyrosine.—These bodies, formed normally in the alimentary canal, are occasional constituents of the urine, more especially in acute yellow atrophy of the liver (p. 126), and in phosphorus poisoning. Leucine and tyrosine have also been found in the urine, in small quantities, in cases of hepatic cirrhosis. It is to be remembered that in this disease widespread degenerative changes occur in the liver-cells, giving rise to a condition sometimes spoken of as secondary yellow atrophy; hence the presence of leucine and tyrosine in the urine is of interest in the pathology both of this malady and of acute yellow atrophy. When these bodies are present the amount of urea is generally much below the normal, and in acute yellow atrophy it may even be absent.

Tyrosine occurs both as crystals and also dissolved in the urine; the

crystals are usually of a greenish colour, and are deposited in the form of sheaves and rosettes. Leucine, on the other hand, is usually found in crystalline globular masses. Crystals of calcic phosphate, of sodic phosphate, and of the lime and magnesium salts of fatty acids, are sometimes found in the urine in the form of sheaves and rosettes, and may be mistaken for tyrosine ; but in the case of the phosphates the individual needle-like crystals are broader, and they are usually colourless. Reliance, however, should not be placed on the crystalline appearance alone, but some tests characteristic of tyrosine should also be employed.

Tests for Tyrosine.—The best known of these are Piria's and Hoffmann's reactions. Tyrosine when heated with Millon's reagent yields a brilliant crimson colour (Hoffmann's reaction).

Tyrosine, if treated with concentrated sulphuric acid and warmed gently, turns pink. The mixture is allowed to stand, diluted with water, saturated with barium or calcium carbonate, and filtered while hot. On the addition of dilute perchloride of iron free from acid, the filtrate yields a violet colour (Piria's reaction).

Leucine is not readily recognised by chemical tests unless a considerable quantity of the pure substance is available, hence in the urine its presence is to be detected by its microscopic characters.

In cases in which leucine and tyrosine are found in the urine, lactic acid may also be present. This is true of the urine of phosphorus poisoning, and also in cases of acute yellow atrophy of the liver. The excretion of lactic acid in the urine, associated with the diminished excretion of the normal nitrogenous extractives in these conditions, resembles the condition brought about experimentally by the removal of the liver in birds ; since after this operation the nitrogenous extractives in the urine fall to a very small amount, and lactic acid and ammonia are excreted.

Salts.—*Sulphates.*—Two grams of sulphuric acid a day are excreted in normal urine, and the bulk of it is excreted in combination with inorganic bases, such as sodium, potassium, magnesium. Some of it, however, is excreted in the form of a double salt, one of these bases being usually potash in combination with certain aromatic bodies, such as phenol, cresol, indole, or skatole ; these form the well-known aromatic sulphates or potassium salts of phenyl-sulphuric acid.

A small quantity of sulphur is also excreted in combination with amides, forming bodies of the taurin (amido-ethyl-sulphonic acid) class. Cystin (dithio-diamido-dilactic acid) is another example of these bodies. The amount of sulphur so eliminated is very small. The sulphates excreted as inorganic and as aromatic sulphates are derived in part from the food and in part from the metabolism of the tissue proteins ; and their main clinical interest lies in the relation between the amounts of the aromatic and the total sulphates. Normally, the proportion existing between the aromatic and simple sulphates is approximately one part of the former to twelve to twenty parts of the ordinary sulphates. The aromatic sulphates are derived mainly from the decomposition of protein

matter, and largely from decomposition and putrefaction in the intestine. Hence the amount of aromatic sulphates excreted is considerably increased in intestinal and abdominal diseases associated with retention and putrefaction of the intestinal contents; as, for example, in intestinal obstruction, and in peritonitis. In enteric fever they are said not to be increased. They are increased in cases in which putrid decomposition of protein matter arises, as in putrid empyema, pulmonary gangrene, and the like. In fact they are necessarily increased in cases of the kind which lead to indicanuria, inasmuch as indigo is present in the urine as an indoxyl sulphate. Aromatic sulphates are also greatly increased in amount in cases of poisoning by carbolic acid.

Cystin and Cystinuria.—This sulphur-containing body is occasionally present in the urine, and it may even give rise to the formation of calculi. It crystallises in flat colourless hexagonal plate-like tables, insoluble in water, alcohol, ether, or acetic acid, but freely soluble in ammonia and mineral acids, and so differing from uric acid. Cystin burns with a bluish-green flame on platinum foil, without first melting. If the crystals are boiled with caustic potash and oxide of lead, sulphide of lead is formed. Similarly, if heated with caustic potash on a silver dish or silver coin, a black mark is left on the silver from the formation of sulphide of silver. Two isomeric forms of cystin are known (Neuberg and Mayer), one derived from the decomposition of proteins, particularly horn or hair, the other being the isomer that forms most cystin calculi.

The main interest of cystinuria is that, like alkapttonuria, it is a "chemical malformation" of the body (Garrod). It is a hereditary and family disease, largely independent of diet, and appears to be due to an abnormality in the amino-acid metabolism. The tissues of the cystinuric patient are unable to complete the oxidation of the cystin normally formed in the breaking down of protein; and many of these patients also shew constantly or intermittently a similar inability to oxidise other amino-acids normally formed in the disintegration of protein, such as leucine, tyrosine, aspartic acid, lysine, or arginine, when these bodies are added to their food. Unlike alkapttonuria, cystinuria is of importance in that it gives rise to the formation of calculi in the bladder and kidney.

Phosphates.—Two to six grams of phosphoric acid are excreted daily in the form of mixed phosphates of potassium, sodium, lime, and magnesium: and the acidity of the urine is dependent mainly upon the presence of acid sodium phosphate. A large quantity (two-thirds to three-quarters) of the phosphoric acid excreted is united with potassium and sodium, and, whether the salts formed be acid, neutral, or basic, they are soluble in the urine, and hence are not seen as urinary deposits.

Earthy phosphates of lime and magnesium are only soluble in acid urine, hence the neutral and basic phosphates of lime and magnesium tend to be deposited in faintly acid, neutral, and alkaline urines. In urines alkaline with ammonia, ammonio-magnesic phosphate is formed, which is also insoluble. Ammonio-magnesic phosphate has been found deposited from urines still faintly acid. The phosphates are derived

largely from the food, partly from the tissues. The amount of phosphates in the urine is largely increased after meals, and then, owing to the diminished acidity or even positive alkalinity of the urine, it is not uncommon for some precipitation to occur ; the amount of deposit, however, is no index to the amount of phosphatic material present in the urine, inasmuch as its deposition depends simply on the reaction. In all cases, if the amount excreted is to be determined, reliance must be placed on quantitative methods of estimation, and not on the amount of deposit. To the clinician the main interest lies rather in the deposit of earthy and of triple phosphates than in the total amount of phosphates excreted ; for the latter depends very largely on the quantity and nature of the food.

Physiological phosphaturia occurs when the diet is rich in alkaline carbonates, or in salts of vegetable acids that are oxidised to carbonates in the body ; it also follows a meal rich in protein, in consequence of the abundant secretion of hydrochloric acid by the stomach during digestion. No trustworthy quantitative experiments appear to have been made upon patients with the so-called nervous phosphaturia ; it is possible that in these cases, too, the condition depends rather upon an anaciduria, and the secretion of an abnormally alkaline urine. In certain cases of juvenile phosphaturia, however, it is certain that the condition is due to an increase in the amount of urinary calcium and a corresponding decrease in the faecal calcium (Soetbeer), the urinary excretion of the other salts, nitrogen, and phosphoric acid itself, remaining normal. It has been suggested, but not proven, that this form of phosphaturia depends upon an inflammation of the intestinal mucosa that prevents it from secreting calcium to the normal extent (Albu and Neuberg) ; the treatment consists in giving a diet poor in calcium salts.

In febrile disease the quantity of phosphates excreted is at first diminished ; later it is increased. It is held that in certain states of neurasthenia the quantity is increased ; and the name of phosphatic diabetes has been given to a condition in which, along with general malaise and various neurasthenic symptoms, large quantities of urine, containing an excess of phosphates, are excreted (*vide* Vol. III. p. 228).

On heating urine faintly acid, neutral, or alkaline, a cloudy deposit of earthy phosphates is produced ; or, if the liquid previously contained a deposit of phosphates, this is increased. If the liquid is not actually raised to the boiling-point, the deposit will redissolve on cooling ; but if it be boiled, the deposit is permanent. If the boiling be done in a sealed tube, the precipitate can be produced and dissolved several times in succession. There are several possible explanations of this : (a) That the boiling drives off the carbonic acid by which the phosphates were kept in solution ; (b) that the boiling causes a decomposition to ensue of such a character that two molecules of dicalcic phosphate and one of monocalcic phosphate undergo an interaction, which leads to the formation of one molecule of triple and one molecule of dicalcic phosphate, the former of which, being far less soluble, is precipitated ; (c) it has also

been suggested that on boiling, sufficient urea is decomposed into ammonium carbonate to render the urine sufficiently alkaline to cause the precipitation of phosphates. It is improbable that the precipitation is simply dependent on the lower solubility of certain phosphatic salts in hot urine than in cold ; and it is more likely that a decomposition of the nature described above ensues. The deposition of phosphates in the urine depends partly upon the amount present, but largely upon the degree of acidity of the urine. The deposition of earthy phosphates—for example, the tricalcic—is associated with an alkaline action due to fixed alkali. This deposit is amorphous, and is often seen after meals. Occasionally stellar phosphate—that is, dicalcic phosphate—is thrown down when the acidity of the urine is diminished ; but it usually occurs in urine still faintly acid, it is rarely seen in neutral or alkaline urines. The crystals are frequently arranged in stars and rosettes, or in sheaf-like bundles, thus offering a distant resemblance to tyrosine crystals. This deposit is rarely seen in healthy urine ; it occurs, however, in the urine of diabetes and of other maladies, such as cancer, which produce grave disturbance of nutrition. In urines alkaline from volatile alkali a deposit of triple phosphate (ammonio-magnesic phosphate) is common ; and this crystalline deposit frequently leads to the formation of a calculus enclosing most usually a nucleus of uric acid or of oxalate of calcium that has been formed in the kidney and passed on to the bladder. This triple phosphate is also prone to encrust the surface of vesical growths ; and it tends to be deposited whenever there is cystitis : the amorphous deposit of tricalcic phosphate, on the other hand, owing to its amorphous character, rarely forms calculi.

Chlorides.—Although these salts play an important part in the economy, and are excreted in the urine in abundance—10 to 15 grams being the amount of the daily excretion of sodium chloride—the variations in the amount of chlorides excreted are not of any great clinical importance, except in so far as the retention of chlorides may affect the production of dropsy, in renal and cardiac diseases (48) (*vide* also p. 525). They depend largely upon the amount of chlorides in the food. The principal point is that the chlorides are diminished during the height of the pyrexia of febrile diseases ; and more especially in pneumonia, in which, during the duration of the fever, they may almost disappear from the urine to reappear again at defervescence and during recovery. The amount present does not afford any valuable indication as regards diagnosis or prognosis of febrile states. Although it is in pneumonia especially that the chlorides undergo this great diminution, the same phenomenon is seen to a less extent in other febrile diseases, and more especially when the fever is high, as in tonsillitis, for instance, so that the diminished excretion is dependent rather on the general febrile process than on the particular incidence of it on the lung. To determine roughly the amount of chlorides present in the urine it is sufficient to acidulate the urine with nitric acid, to add a few drops of nitrate of silver, and to compare the precipitate obtained with the amount obtained by a similar procedure

with normal urine. If necessary, the precipitate of chloride of silver may be collected and weighed in the usual manner employed in quantitative determinations.

Oxalates.—About 10 milligrams of oxalic acid are excreted daily in the normal urine in the form of a salt kept in solution by the acid phosphate of sodium normally present. Oxalates are deposited in the urine in the form of oxalate of calcium, which tends to crystallise either in octahedra, or as dumb-bells or ovoids. The crystals are visible to the naked eye as brilliant points, and usually crystallise like uric acid on any irregularities, such as scratches, on the glass vessels in which the urine is contained. Urine depositing oxalate of lime is usually acid, rarely neutral. The dumb-bell form of crystals deposited is perhaps due to the disturbance of the form of crystallisation by mucin and other colloids present. A scanty deposit is not unusual in health, and more especially after certain articles of diet, such as rhubarb and other vegetables. A persistent deposit, however, is pathological, although it is not clear upon what this oxaluria depends. The name oxaluria ought, of course, to be restricted to an increase of the excretion of oxalic acid, and not simply to its deposition. In many cases the increased excretion or deposition of oxalic acid may lead to the formation of an oxalate of lime calculus, without the production of any other symptoms except those due to the stone. In other cases the persistent excretion of these insoluble oxalates is accompanied by a series of symptoms of a dyspeptic character, together with some mental depression, neurasthenia, or even actual hypochondriasis, and it is not clear whether there is any definite cause of association between the two sets of phenomena, although many observers regard the dyspeptic, nervous, neurasthenic symptoms as primarily due to the oxaluria. The bulk of the oxalic acid excreted in the urine is derived from the food, but it is possible that traces are formed by the metabolism of the tissues, since oxalates do not entirely disappear during starvation. Its production in the body is favoured by the absence of free hydrochloric acid from the gastric juice and by the presence of increased intestinal fermentation.

Albuminuria.—The name albuminuria is generally taken to signify the presence of protein matter in the urine. The proteins met with in the urine are serum albumin, serum globulin, albumose, peptone, fibrin, nucleo-albumin, and perhaps occasionally a casein-like body, and, if blood or blood pigment be present, haemoglobin. In health the urine is free from any large quantity of protein matter, although in a large but variable number of persons apparently healthy the urine is found to contain protein matter in small quantities. To this condition the name of *physiological albuminuria* has been applied. This albuminuria is, in some of the cases, always present; in others, it appears only under certain conditions, as, for instance, on first rising in the morning, after a cold bath, or after meals, and more especially after severe exercise. Some of these varieties have received special names; such as intermittent albuminuria, dietetic albuminuria, postural and cyclic albuminuria.

Orthostatic albuminuria disappearing when the patient lies down has been attributed to abnormally low blood-pressure by Edel and by Loeb; it has been shewn that the renal functions may be unimpaired in these cases, and that the albuminuria may be connected, in some instances, with a diminution in the coagulability of the blood, and may be made to disappear by the administration of calcium salts (A. E. Wright and Ross).

Albuminuria is either "physiological" or pathological; by the former it is understood that in apparently healthy persons albumin—usually in small quantity—is found in the urine; sometimes so little that it requires special tests, such as picric acid, to reveal it; at other times it is in sufficient quantity to yield a distinct precipitate with the heat test or with cold nitric acid. In these cases it is important to exclude what may be called accidental albuminuria—cases, that is, in which the urine itself, originally free from albumin, has been contaminated by some albuminous impurity; as in gonorrhœa, vaginitis, and seminal discharge.

Probably in no case of so-called physiological albuminuria is the quantity so large as to amount to one-third or even one-fourth of the urine. This albuminuria in the apparently healthy is not necessarily continuous. It may be seen only after meals, and more especially after breakfast, or on first rising in the morning, or after severe exercise. It is supposed in many cases to depend upon a vascular disturbance in the kidney, leading to temporary venous congestion; and in the dietetic cases it has been thought that digestive products, such as albumoses, might be formed, either in greater abundance than usual, or else of abnormal quality, and, absorbed as such, be subsequently excreted by the kidney. It is extremely doubtful, however, whether all such cases of albuminuria should be called "physiological." It is quite possible that, in many such cases, no serious kidney lesion is present, nor yet, perhaps, any condition likely to eventuate in a serious kidney lesion; yet, on the other hand, such kidneys cannot be considered quite normal. In a considerable proportion of cases of "physiological albuminuria" the use of the centrifuge shews that the urine contains definite formed elements, such as white blood-corpuscles, casts, spermatozoa and so forth. In other words, the presence of casts in small amount is not restricted to "pathological albuminuria." An important form of physiological or functional albuminuria is that seen after severe exercise. A large proportion of athletes in vigorous health and in training shew the presence of a considerable quantity of albumin in the urine after a severe race, especially running races and rowing (Collier). This albuminuria is transitory, and cannot be regarded as indicative of the presence of any renal lesion. In the postural form the albuminuria disappears so long as the recumbent posture is maintained, and, what is more remarkable, disappears in the later hours of the day, notwithstanding the maintenance of the erect posture. It must be remembered that in renal cirrhosis the urine may contain only traces of albumin; and the possibility of the presence of this insidious disease in some cases of so-called functional albuminuria must be kept in view.

Pathological Albuminuria.—Albuminuria may be due to disease of any part of the urinary tract, such as pyelitis or vesical disease; but in these cases, to speak strictly, the albuminuria is factitious and is due to admixture with albumin after the urine has left the kidney. When the albuminuria is of renal origin, the albumin transudes into the urine, owing to some definite lesion, temporary or permanent, of the kidney epithelium. Sometimes the kidney lesion is primary, at other times it is secondarily induced by the ingestion or production of toxic and irritating substances in other parts of the body. At other times, again, the changes in the kidney are dependent upon other secondary disturbances; thus the following causes of albuminuria may be recognised:—(a) Congestion of the renal vessels, active or passive. (b) Toxic or febrile albuminuria. (c) The albuminuria of organic renal disease, such as acute nephritis, chronic Bright's disease.

(a) Active Congestion.—The loss of albumin in this condition is usually not large, as the quantity of urine secreted is small and often blood-stained. It is difficult to distinguish the albuminuria of active congestion from that due to toxic agents, as in many cases poisons, such as turpentine and cantharides, produce extreme congestion. The albuminuria of acute Bright's disease is usually quoted as an instance of this form of albuminuria.

Passive congestion is a frequent cause of albuminuria, more especially in heart and lung diseases, and as the result of various abdominal diseases leading to pressure on the renal veins or vena cava. Passive congestion causes a considerable diminution in the quantity of urine excreted, and this may contain blood and blood-casts. In cases of pressure on the renal veins from abdominal diseases the percentage amount of albumin present may be large, but in cardiac and pulmonary cases the quantity is usually small. From the mere amount of albumin, however, no conclusion can be drawn as to whether the albuminuria be due to passive congestion or to nephritis. It may be large in the former and small in the latter, or conversely. Blood may be present in either case. The question is best answered by the character of the casts present. In passive congestion blood-casts and hyaline casts are occasionally found; in nephritis, on the other hand, casts containing definite renal elements are found.

(b) Febrile or Toxic Albuminuria.—This is dependent, in all probability, on the excretion by the kidney of toxins produced by the organisms causing the disease. These toxins apparently lead to changes in the renal epithelium, glomerular and tubal, and thus allow the proteins of the blood-plasma to pass out. In this way the febrile albuminuria resembles the albuminuria produced experimentally by the injection of egg-albumin, albumoses, or peptones. The protein matter found in the urine subsequent to this procedure is not only the albumose or other protein injected, but also the protein matter of the blood-plasma; and the amount of protein recoverable from the urine is frequently far greater in amount than the quantity injected. Thus the albuminuria brought about by the intravenous injection of these protein substances resembles the albuminuria

due to such poisons as cantharides. On the other hand, many toxins produced in disease apparently do not cause the extreme congestion that is seen with such poisons as cantharides. In scarlet fever the early albuminuria of the disease, which is of this nature, must be carefully distinguished from the later albuminuria dependent upon nephritis often persistent and progressive. The kidney lesion that produces the albuminuria of febrile diseases, often spoken of by French writers as transitory nephritis, is remarkable, inasmuch as this lesion generally disappears completely, leaving the kidneys practically healthy. In this respect the initial albuminuria, or so-called febrile albuminuria, of scarlet fever is strikingly different from the later albuminuria, which is dependent on a progressive and destructive lesion in the kidney. In the great majority of cases the changes produced in the kidney by these toxins do not lead to permanent Bright's disease; and the albuminuria of typhoid, scarlet fever, diphtheria, and pneumonia usually clears up entirely. Occasionally in typhoid fever, diphtheria, and pneumonia, and very frequently in scarlet fever, there is a further and more severe lesion produced in the kidney, and the case becomes one of acute or subacute nephritis, with dropsy and suppression of urine. Hence it is difficult to draw a hard and fast line between the febrile albuminuria produced by toxins, or the *néphrite passagère* of the French, and a permanent and often progressive lesion like Bright's disease.

In some febrile diseases the urine, besides serving as a channel of excretion for toxins, contains also the organisms causing the disease. This is not uncommon, for instance, in typhoid fever; and it is probable that in all diseases in which the organisms circulate freely in the blood-stream they may be detected in the urine.

In some febrile diseases, more especially in pneumonia and in cases of suppuration, such as empyema and cerebrospinal meningitis, albumoses are present in the urine in comparative abundance, but rarely alone, serum albumin and globulin being also present. The albumoses are formed in the exudation produced at the seat of the disease, for instance in the solidified lung of pneumonia, or in the purulent exudation of empyema, they are absorbed by the blood and are carried to the kidney, where they are excreted.

(c) Albuminuria of Renal Disease.—In Bright's disease the albuminuria is due to the damage and the shedding of the renal epithelium in the glomeruli and tubules. Some authors regard the change in the kidney structures as primary and brought about either by vascular changes, as in Bright's disease due to cold, or by toxic agencies, as in the Bright's disease due to alcohol, and in the sequel of acute specific maladies, such as scarlet fever and pneumonia. Others look upon many forms of Bright's disease as being due to a disease of the blood, and hold that the kidneys are affected secondarily to this blood change. However this may be, the immediate cause of the albuminuria is the anatomical change in the renal epithelium.

Even in renal cirrhosis, in which the albuminuria has been attributed to

the high blood-pressure, it is more probably due, perhaps, to the accompanying epithelial lesions; for although the main lesion is in the interstitial tissue, yet in this disease there are always considerable tubular and glomerular changes.

In renal disease the actual amount of protein matter found in the urine varies within very wide limits, being least in renal cirrhosis in which there is sometimes but a trace, and rarely more than a few grams in the twenty-four hours. On the other hand, in some forms of chronic Bright's disease, and in certain forms of lardaceous disease of the kidney, the amount may reach 40 grams a day. In acute Bright's disease, although the percentage of protein matter in the urine is high, the amount lost is not very great, owing to the small amount of urine secreted. In the small white contracted kidney the amount of albumin lost is often considerable, amounting not infrequently to as much as 20 grams daily. In diseases of the pelvis of the kidney, as in calculous, suppurative, or tuberculous pyelitis, the albumin in the urine, from the mere presence of pus or blood in the urine, is often considerable; and it is often of great moment to determine whether the albuminuria be due merely to the products of the pyelitis, or whether there is coexisting renal disease. In the latter case the amount of albumin in the urine may still be considerable after the pus or blood has been removed, either by subsidence or by the centrifuge. Again, if the albumin be of renal origin the urine will probably contain renal casts. In all such cases, however, the pus, blood, and other impurities should be removed from the urine before the latter is tested for albumin. In renal diseases the proteins are usually present as a mixture of serum albumin and serum globulin. Hoffmann defined the ratio of the albumin to the globulin as the albumin quotient, and in nephritic patients the value of this quotient varies from 1·5 to 2·3 as a rule. Its values may differ widely in the same patient on different days. It appears, however, that the serum albumin generally predominates in cases of granular kidney (Czetary), whilst the serum globulin is relatively increased in cases of acute or chronic parenchymatous nephritis (Cloetta). In lardaceous disease of the kidneys, too, the globulin may equal or even exceed the albumin in the urine.

Albumosuria.—Two distinct forms occur:—(a) The rare but extremely interesting condition of hetero-albumosuria in which Bence-Jones protein is found, sometimes in such large amounts as 7 per cent, in the urine in cases of multiple myeloma (Kahler's Disease, *vide* Vol. III. p. 77). It is closely related to albumin, and is precipitated at a low temperature, 58° C.

(b) Deutero-albumosuria seen in pneumonia, suppurative and auto-lytic processes, gastric and intestinal ulceration, and in renal disease especially when due to syphilis. In renal disease serum albumin and serum globulin may be present in the urine in association with albumose. These cases of albumosuria in renal disease are rare, and their nature and cause are obscure, since the presence of considerable quantities of

albumose in the urine is usually the result of absorption of the albumose from some inflammatory exudation into the blood ; but in renal cirrhosis the albumosuria occurs without the presence of any inflammatory complication. It is possible that the albumose may be derived from the intestine. Von Noorden points out that albumoses may be formed in albuminous urine after it has been passed, either by bacterial action or by the action of pepsin which is always found in the urine of nephritic patients (Mya and Belfanti).

Nucleo-albumin and Mucin.—Clinically a clear chemical distinction is rarely drawn between the “ nucleo-albumin ” and the “ mucin ” or mucin-like substances called mucoids by Hammarsten that occur in the urine. In small quantities these bodies remain in solution as normal constituents of urine ; when present in larger amounts they are usually precipitated spontaneously, and the precipitate is taken to indicate some catarrhal affection of the urinary tract, or, in women, of the vagina. Such urine is usually turbid when passed, depositing a bulky cloud (the “ nubecula ”) or even a viscid, gelatinous, or mucoid sediment on standing ; leucocytes, epithelial cells, and crystals are often seen in this deposit. Urinary nucleo-albumin is insoluble in pure water, and is precipitated from its saline solutions by acetic acid unless an excess of salts is present. Its quantity is increased in nephritis ; its presence may be suspected in urine if in the performance of Heller's test a hazy ring of precipitate forms about a third of an inch above the level of the nitric acid, or if the addition of a little acetic acid causes the urine to become opalescent or even opaque, or if the urine after dilution gives a more marked high ring in Heller's test than the undiluted specimen does, or, finally, if the addition of a little dilute acetic acid to the dialysed salt-free urine causes the precipitation of a substance soluble in alkaline or saline solutions. This urinary nucleo-albumin is probably a mixture of the compounds formed by the union of albumin mainly with chondroitin-sulphuric acid, to a less extent with nucleic acid, and in cases of jaundice with taurocholic acid also (Mörner) : the identification of these substances is naturally a very complex chemical process. In testing an albuminous urine for nucleo-albumin it is well to remove most of the albumin by boiling and filtering ; the filtrate may be tested with acetic acid after it has cooled. True mucin is found in the urine very rarely (Hammarsten) ; the “ mucin ” or “ mucus ” so commonly described in urine is almost always the “ nucleo-albumin ” composed as has been described above.

Protein Tests.—The ordinary tests in use for the recognition of proteins in the urine are (α) the heat test ; (β) the cold nitric acid test (Heller's test) ; (γ) the picric acid test ; (δ) the copper sulphate and caustic potash test ; (ϵ) the salicyl-sulphonic acid test.

(α) The heat test is perhaps the one most commonly used, inasmuch as it is simple, open to few fallacies, and fairly delicate. In performing this test the reaction of the urine must be previously ascertained ; and, if necessary, it should be rendered faintly acid with acetic acid before boiling. Some authors prefer to add the acid after boiling ; but it is

probable that in this way small quantities of protein matter may be overlooked. If the urine is not acid at the time of boiling, the protein matter is liable to be converted on heating into alkali albumin, which is not coagulated by heat, and thus the presence of small quantities of protein matter may be overlooked. It is no less necessary to avoid over-acidity of the urine, for in such urine, particularly if rendered acid with a strong mineral acid, the protein coagulated may subsequently be redissolved. The principal fallacy in the heat test, however, is the precipitation of phosphates on warming faintly acid or neutral urines. This cloudiness is usually distinguished from the precipitated albumin by the particulate form of the latter: further, the phosphatic cloud disappears instantly on acidification; the protein precipitate, on the other hand, does not.

(β) *The Cold Nitric Acid Test.*—This is an excellent test, if properly performed; but it is not quite so delicate as the heat test. The nitric acid must be pure, and, after being placed at the bottom of the test-tube, the urine to be tested should be floated on its surface with a pipette. If protein matter is present in abundance, a ring is formed at once. If the amount is small, the ring only appears after standing. The fallacies of this test are as follows:—Protein matter, if present, may be missed if the urine and the nitric acid are mixed up; hence nitric acid causing any effervescence of the urine, owing to the presence of nitrous acid, is not suitable for this reaction. Protein matter, even if not present, may be suspected if a crystalline deposit of nitrate of urea be formed at the junction of the urine and the acid; this deposit is more apt to occur in concentrated urines, and the mistake is easily avoided by noting that the ring is crystalline in appearance. Occasionally mistakes arise from the formation of a dense highly-coloured ring at the junction of the urine and the acid. This ring (see p. 538) is due to the formation of pigment from a chromogen present in the urine: it is coloured and not particulate; the protein ring, on the other hand, is white and particulate. By the nitric acid the presence of albumoses can be detected, bodies which are not brought into evidence by heat.

Many resinous bodies after their administration are excreted in the urine, and these substances, on the addition of an acid, yield a precipitate that may be mistaken for albumin. This is especially true of copaiba and of oil of turpentine. The precipitate can be distinguished from protein by its solubility in alcohol; but the addition of alcohol to nitric acid may cause an explosion.

(γ) *Picric Acid.*—A cold saturated solution of picric acid is a useful test for proteins, and it has the advantage that it can also be used in testing for sugar. The addition of picric acid to a urine containing proteins is followed by the formation of a cloudiness or a copious precipitate, according to the amount of protein matter present. From a clinical point of view the only serious objections to the picric test are that, in the first place, mucin is precipitable as well as ordinary proteins; and, secondly, that, as a protein test, it errs on the side of delicacy: quantities of protein

are discovered by it which, at any rate, are of no serious clinical importance.

Picric acid is the agent that is more especially used in the investigation of cases of so-called physiological or functional albuminuria.

(8) *Copper Sulphate and Potash*.—Copper sulphate and potash are reagents sometimes used in testing the urine, and the value of this test is that, whereas it yields a rose colour with albumoses, it gives a violet colour with ordinary proteins ; in fact, for the detection of small quantities of albumoses this test is, on the whole, preferable to the nitric acid test.

(e) *Salicyl-sulphonic Acid*.—This reagent is intermediate in delicacy between Heller's test and the heat and acetic acid test. A cold saturated solution of salicyl-sulphonic acid in water is used, and is added to the suspected urine in the quantity of one to three drops ; an excess of the reagent, however, does not interfere with the test. The fluid is then well shaken. An immediate precipitate betokens the presence of an appreciable amount of protein. If the precipitate does not fall in from one to two minutes the quantity of albumin is minimal ; and if an interval be allowed to elapse, the test is really more delicate than the heat and acetic acid test. Normal urines give no precipitate with this reagent. This test is also of use for recognising albumoses and peptones, inasmuch as with these substances precipitates are obtained which dissolve on heating and reappear again on cooling.

Salicyl-sulphonic acid does not give any precipitate with bile salts, with urates, with alkaloids, nor with urine containing copaiba resin. With a large amount of mucin, however, a small amount of precipitate is obtained. This test is well worth the attention of clinicians.

Sometimes it is necessary not only to detect the various proteins present in the urine, but also to determine the relative quantities present. For this purpose the proteins must be precipitated with neutral salts ; by saturating the urine with ammonium sulphate all protein matter except true peptones are precipitated. On the other hand, magnesium sulphate is used to precipitate serum globulin alone, as it does not cause any precipitation of serum albumin or of albumoses. When the salts are used to precipitate proteins from the urine it is of course necessary to wash the precipitated protein on the filter-paper with the saturated solution of the salt used. Thus, a precipitate of albumose obtained with ammonium sulphate must be washed with a saturated solution of ammonium sulphate. At the present time the precipitation of protein matter in the urine by these solutions of neutral salts is used more for the purpose of research than of clinical routine.

Quantitative Estimation of Protein.—For rough estimations the amount of precipitate deposited at the bottom of the test-tube in twenty-four hours after acidification with acetic acid and heating is usually sufficient. This rough method, however, is liable to considerable error, owing to various conditions of the urine, such as its acidity for example, influencing the retractility of the coagulum.

If this method is employed, the amount of protein is usually expressed in a fraction of the volume of the urine. A more accurate method is that of Esbach, in which the urine is precipitated by a solution containing picric acid, and the amount of protein is determined by the bulk of the deposit precipitated in a specially graduated tube. Esbach's method, although more accurate than the previous one, is open to a similar fallacy; and the only really accurate method is to precipitate the protein and, after washing and drying the precipitate, to weigh it. The most convenient method of doing this, if the urine contain a considerable amount of protein, is to add 5 c.c. of the urine to some 50 c.c. of boiling absolute alcohol. The mixture is allowed to remain in a hot-air oven at 80° C. for some hours, the precipitate is collected on a weighed filter-paper, washed with alcohol, ether, and water to remove the salts and fats, dried in the hot oven at 120° C. and weighed; if further control is desired, the total nitrogen in the precipitate can be determined by Kjeldahl's method.

Albumoses, and especially hetero-albumoses, which are the kind commonly present in the urine, form a precipitate on the addition of nitric acid. In testing for albumoses it is often better to add the nitric acid drop by drop to the suspected urine rather than to float the urine on the nitric acid. The characteristic reaction of albumose, however, is that the precipitate, formed by nitric acid, dissolves on heating, to reappear on cooling. The reaction is so characteristic that it may even be possible, although not advisable, to carry out the test in the presence of other protein matter; as in these circumstances, if the quantity of albumose present be considerable, the coagulum produced by the nitric acid will diminish in amount on heating, to increase again on cooling. It is better, however, to remove the serum albumin and serum globulin, either roughly by heating, or by precipitation with some neutral salt before testing the filtrate for albumoses with nitric acid.

Pyuria.—Pus may be present in the urine as the result of diseases of the urinary tract; as in suppurative nephritis, pyelitis, cystitis, or urethritis, or from rupture into the urinary tract of an abscess outside it, as in perinephritic or prostatic abscesses; or, finally, the urine may contain pus by simple contamination from a pus-secreting surface, as in cases of vaginitis. In all cases of pyuria it is important first to see the urine passed, and, secondly, to have it passed in at least two portions. In this way it is possible to separate the cases in which the pyuria is of renal origin from cases of pyuria of urethral origin. Further, it is very important to separate the pus from the urine either by subsidence or, preferably, with the centrifuge before testing the supernatant clear urine for albumin. In this way it is possible to determine with certainty the presence or absence of organic renal disease in relation to the disease causing the pyuria. In cases of calculous pyelitis it is not uncommon for serious renal disease to be present in addition to the pyelitis. Abscess of the kidney, with or without perinephritic abscess, and pyelitis leading to pyonephrosis, may be and frequently are present without the urine containing any pus. In fact, the absence of pus from the urine is a matter

of comparatively small importance in the diagnosis of pyonephrosis in the presence of a renal tumour. Pus present alone in the urine, unless the amount of it be very large, does not cause more than a trace of albumin. Hence the appearance of a considerable amount of albumin in the urine containing pus is always suggestive of the coexistence of renal disease. The presence of casts containing renal elements will also assist us in forming this diagnosis. Urine containing pus may be acid or alkaline ; the former is more characteristic of the pyuria of renal origin, the latter of that of vesical origin.

If, however, cystitis be slight in amount the urine may remain acid, as in some cases of pyelitis ; on the other hand, in pyelitis complicated with cystitis the urine may be alkaline. Hence, in the differential diagnosis, too much stress must not be laid on the reaction of the urine. In acid urine the pus corpuscles are discrete and subside ; in alkaline urine the pus isropy and stringy. Pus is best recognised by microscopical examination, but the suspected urine, if acid, may be tested by the addition of liquor potassae, which causes any purulent deposit to become ropy. Ozonic ether causes an effervescence in urine containing pus.

Chyluria, or the appearance of fat, albumin, and sometimes also fibrin in the urine, is a disorder rarely seen except in those who have resided in tropical countries (see Vol. II. Pt. II. p. 940).

Lipuria, or the passage of urine containing droplets of fat, has been observed in patients suffering from such various conditions as diabetes mellitus, phosphorus poisoning, recent fractures of the long bones with liberation of the medullary fat, and chronic nephritis with extensive fatty change in the renal epithelium. It may also occur almost physiologically in the urine of pregnant women, or in that of persons who are taking large quantities of olive oil by the mouth (alimentary lipuria). Urine containing fat is turbid or even milky when passed, and the fatty globules in it can be recognised under the microscope ; the turbidity clears up when the urine is shaken with ether, and the ethereal extract leaves a greasy residue of the fat on evaporation. The quantity of fat in lipuria varies up to as much as 3 per cent.

Fibrinuria is occasionally met with in patients with haematuria or chyluria, or as a consequence of an acute inflammation in the urinary tract. It has also been met with as a terminal event in a case of chronic parenchymatous nephritis (Emerson). The urine in this condition contains fibrinogen, and clots spontaneously either before it is passed or on standing.

The pathogenesis of glycosuria is fully dealt with in the article on Diabetes Mellitus (Vol. III. p. 172), and the tests for dextrose in the urine are described in the same article (p. 188), to which the reader should refer.

Glycuronic acid is an intermediate product formed in the oxidation of dextrose, and possibly of protein and fat (Mayor and Neuberg). In normal urine it has been found to the extent of 1 part in 25,000

(Neuberg), appearing there only when it has been saved from further oxidation by combining with organic bases in the body. These bases may be compounds produced normally in the tissues, such as indoxylo, skatoxyl, indole, and various alcohols or phenols. Or they may have been introduced into the body in the form of drugs, such as phenol, chloral, butyl-chloral, morphine, antipyrin, antifebrin, pyramidon, camphor, turpentine, acetone, benzene, naphthalene. The resulting "paired" or "conjugated" glycuronic acid compounds undergo no further change in the body, but are excreted by the kidneys *in toto*; it is argued that glycuronic acid is of great importance to the organism by neutralising and securing the excretion of the numerous endogenous and exogenous poisonous substances mentioned above. The glycuronates are laevo-rotatory, reduce Fehling's solution rather slowly on boiling, and do not ferment with yeast. After being boiled for half an hour with 5 per cent sulphuric acid, their solutions become dextro-rotatory from liberation of the dextro-rotatory free glycuronic acid. (For Acetone and Diacetic Acid see Vol. III. pp. 190, 469.)

Laevulosuria.—Laevulose, or d-fructose, is often present in the urine of patients with diabetes mellitus; pure laevulosuria is very rare, producing no special symptoms and not tending to advance. Laevulose is laevo-rotatory when examined in the polarimeter; its chemical reactions are for the most part those of dextrose, and its exact recognition is a matter of some chemical complexity. Alimentary laevulosuria, or the appearance of laevulose in the urine after the administration of 100 grams of the substance by the mouth, has been employed as a test in the diagnosis of functional disorders of the liver (Strauss, Landsberg); it is also seen in many diabetics, and in pregnant women (Brocard).

Lactosuria.—Lactose is habitually found in the urine of women during lactation, usually only in small amount. Lactose is dextro-rotatory, but differs from dextrose in not fermenting with ordinary yeasts, and in giving a yellow or brown colour with Rubner's test, whereas dextrose gives a red colour. The limit of assimilation of lactose by the organism is low, hence alimentary lactosuria is readily produced by the addition of lactose to the diet.

Inosituria.—Inosite, or hexahydroxybenzene, is an aromatic compound and not a carbohydrate. It is found in many of the tissues of the body, and a trace of it is said to occur normally in the urine (Blumenthal). It has been observed in larger, but still small, amounts in the urine of a few nephritic and diabetic patients, but its appearance here appears to be without any definite clinical significance. Its recognition by chemical tests is a process of considerable complexity.

Pentosuria.—Numerous pentoses, or sugars containing a chain of five carbon atoms in their molecules, have been shewn to exist in traces in the urine, both in health and disease (morphinism, diabetes). The pentoses are not readily assimilated in the human body; their excretion in the urine has often been discovered only by accident, and is not necessarily accompanied by any signs or symptoms of disease. It may

be suspected if a specimen of the urine reduces hot Fehling's solution slowly, does not ferment with yeast, has no influence on plane-polarised light, and produces a phenylosazone melting at 160°-166° C. (Neuberg).

Cammidge's pancreatic reaction is described on p. 284.

B. THE KIDNEYS

Physiological Considerations.—The kidneys share with the skin, the lungs, and the intestines the duties of eliminating from the body substances, either produced in the course of metabolism or introduced from the outside, which are either no longer useful or positively injurious.

In health the excretion of the urinary pigments may be instanced as illustrating the former, and the various nitrogenous extractives and salts as illustrating the latter. In disease, the removal of sugar in diabetes illustrates the excretion of a substance no longer useful; and the toxins excreted in the urine in microbial diseases afford an illustration of substances injurious to the economy. In the course of this process in health a considerable quantity of water is eliminated by the kidney; approximately 50 per cent of the quantity ingested. The great bulk of substances excreted in the urine are formed in other parts of the body, and the kidneys are only concerned in their removal from the blood-stream. Some constituents of the urine are, however, undoubtedly formed in the kidney.

The functions of the kidney may be classified somewhat as follows:—

- (i.) The excretion of water.
- (ii.) The excretion of salts, pigments, extractives.
- (iii.) The synthesis of some constituents of the urine.
- (iv.) The metabolic activity.

i. The Excretion of Water.—The excretion of water by the kidney is intimately related to the state of the circulation in the kidney, and as yet there is no definite experimental evidence of any kind of influence of the nervous system on the water excretion, except the indirect one exerted through the vasomotor system.

Broadly speaking, the elimination of water depends on the rate of the flow of the blood through the glomerular tufts, and most substances normally present in the urine, when introduced into the circulation, bring about a dilatation of the renal blood-vessels. Some substances, however, such as digitalis, cause an increased flow of urine, notwithstanding that they produce constriction of the renal vessels. This, however, is dependent on the fact that, along with the renal constriction, there is general vascular constriction; and the heightened blood-pressure so produced causes an increased flow of blood through the kidney. In pathology it is important to bear in mind that the rate of the flow of blood through the kidney is of more importance in determining the actual amount of water excreted than the actual blood-pressure. Although there is no

definite proof of the existence of renal nerves apart from vasomotor nerves, yet it is possible, if not probable, that such exist. Many operative procedures, such as the placing of a cannula in the ureter, bring about complete arrest of the urinary secretion. It is difficult to suppose that this is due to a vascular effect, as oncometric observations do not shew that such operations produce any direct and sudden effects on the volume of the kidney.

Some observers have thought that the kidney reabsorbs water; in other words, that the urine, as secreted by the glomeruli, is more dilute than that passed out from the renal pelvis; and the facts of comparative anatomy as regards the structure of the kidney in different animals are appealed to in support of this opinion.

The amount of water excreted apparently depends also on the amount of kidney substance. This conclusion is based upon the consideration of the following facts:—If a portion of one kidney be excised, the operation is followed by an increase in the amount of urinary water. This increase is not seen after simple incision and suture of the kidney; to produce it a portion must be removed, although the effect is seen when the portion removed is small, weighing perhaps but a few grams. If, after the removal of a portion of one kidney, the second kidney be also removed entire, leaving the animal with less, therefore, than one kidney, the increase in urinary water is very considerable, amounting frequently to twice the normal quantity. No other profound effect is seen, provided the amount of kidney left approximates to one-third of the previous total normal kidney weight. This increase in urinary water, as far as my observations go, is a permanent one; at any rate it persists for periods of four to six months. The removal of a wedge from each kidney produces a very great increase in urinary water, often greater than that seen in the previous series of experiments. In some cases the flow has been quadrupled. This condition is also very persistent, but is not followed by any marasmus or marked deterioration in the health of the animal; the only striking phenomenon being the abundant dilute urine, approximating in character to that seen in the human subject in cases of renal cirrhosis and diabetes insipidus. No cirrhosis or interstitial inflammation of any kind is induced in the organ as the result of these excisions; therefore the increase in the urinary water is in no way dependent upon any secondary pathological process started in the kidney by the operation. Apparently no such increase ensues on removal of one entire kidney. Division of the renal plexus is not followed, so far as my observations go, by any permanent increase in the urinary flow; and division of the renal plexus has no influence in modifying the results produced by the excision of portions of the kidney. It is immaterial in such experiments whether the renal plexus be divided or not.

I am not prepared to offer any explanation of the increased urinary flow, but it is possible that the partial ablation of a kidney produces secondary effects on the blood-pressure, and that this is raised. It is also possible that there is a greatly increased rate of flow through the

fragment of kidney left, and that in this way the elimination of water is increased. It is also possible, but not probable, that the increased flow depends on a diminished reabsorption of water; but the fact that the greatest and most marked effects are seen after partial bilateral nephrectomy is in favour of the dependence of the phenomenon on some secondary effects produced on the vasomotor system.

The kidney is enormously vascular, and is one of the most useful organs in the body for the investigation and demonstration of vasomotor phenomena.

The kidney in animals (dog) receives its vasomotor nerves from the sixth dorsal nerve to the third lumbar inclusive; that is to say, from a consecutive series of eleven nerve-roots, inasmuch as the dog has thirteen pairs of dorsal nerves. It is, however, only the lower of these nerve-roots that contain an abundant supply of vasomotor nerves. Although the great bulk of nerves distributed by these roots are vaso-constrictor nerves, yet there is definite experimental evidence that the lower dorsal and upper lumbar roots contain some vaso-dilator fibres. Further, the kidney receives from the posterior roots a number of afferent nerves, the excitation of which, by producing constriction of large vascular areas, causes a very great increase of the general blood-pressure. It is remarkable that nerves, the excitation of which causes a fall of blood-pressure by bringing about general dilatation, for example, the depressor nerve, the central ends of the lower intercostals, etc., do not produce any marked direct fluctuations in the volume of the kidney.

ii. **The Excretion of Salts, Pigments, etc.**—Although these are grouped together, they are excreted by different portions of the kidney; thus the salts—and certainly the abnormal pigments—are excreted by the glomeruli: the urea, on the other hand, is removed by the tubules. The urea is definitely known not to be formed in the kidney, but simply to be removed. The blood normally contains (approximately) 0·015 per cent, and thus the selective activity of the renal epithelium may be gauged, inasmuch as the urine contains approximately 2 per cent of urea. Although the renal epithelium has such marked selective affinity for eliminating urea, the kidney is able to remove a number of substances introduced into the general blood-stream, especially when such substances are abnormal constituents; but, on the other hand, it will also eliminate normal constituents of the blood-stream not usually present in the urine in cases of a marked increase in such substances. Thus, the abnormal presence of albumoses in the blood is followed by their prompt excretion by the kidney. The same applies to the presence of bile pigments in the blood. A normal constituent of the blood, like sugar, which is normally present in the urine, only in the merest trace, appears readily in this fluid when the percentage in the blood increases from the normal 0·09 per cent to 0·3 per cent. Nothing demonstrates the selective activity of the renal epithelium better than the fact that, although there is in the blood some four or five times as much sugar as there is urea, the urine contains either no sugar or traces at most; whereas, as mentioned above, the

percentage of urea is at least one hundred times greater than in the blood. Although most of the constituents of the urine are derived either from the products of the metabolism of the tissues, or from the ingestion and absorption of various food constituents, some of the urinary constituents reach the urine by a roundabout course ; thus the aromatic sulphates of the urine are derived principally from the decomposition of protein matter in the intestine, and it is certainly remarkable that these substances should be absorbed from the intestine and subsequently excreted by the kidney. Hence the eliminating functions of the kidney are not only related to those of the skin, but are in connexion with the intestine also ; so that it is quite conceivable that, if the eliminating functions of the kidney should be seriously impaired, an accumulation of more or less toxic materials might occur in the intestines ; and this independently of the fact that when the urinary flow ceases, excretion of urea, and probably of other bodies, takes place by the mucous membrane of the stomach and the bile.

Most substances readily excreted by the kidney produce at the same time a copious flow of urinary water, and onometric observations shew that such substances produce vascular dilatation of the kidney.

iii. The Synthesis of some of the Constituents of the Urine.—The urine contains traces of hippuric acid. In many animals the quantity is considerable. In man the quantity is greatly increased as the result of the ingestion of substances containing benzoic acid or its compounds. It is definitely known that when benzoic acid is ingested, it is excreted as hippuric acid, and that the conversion of benzoic into hippuric acid occurs in the kidney. This is important as shewing that the kidney is capable of synthesising complex organic substances ; and what is true of hippuric acid may be true for other urinary constituents.

It has been asserted (Luff) that uric acid is formed in the kidney and not, as is more commonly believed, in the liver or spleen. This conclusion is largely based on the difficulty of determining the presence of uric acid in the blood, even in the cases of animals, such as birds, whose urine contains large quantities of uric acid. The blood of such creatures has long been known to contain urea (Garrod), and it has been supposed that the kidney is concerned in the conversion of urea into uric acid. The removal of the liver in such animals, however, is followed by a very great diminution in the uric acid excreted, and most physiologists consider that this points to the conclusion that the liver is the organ in which the uric acid is formed. Further, the removal of the kidneys in birds, or their destruction by repeated injections of bichromate of potassium (Ebstein), is followed by the deposition of uric acid in various tissues and organs of the body.

iv. Metabolic Activity.—Recent physiological observations have shewn that the suprarenal, thyroid, and pancreas are glands possessing internal secretions ; and a series of observations have been made by myself to see whether the kidneys possess any such functions. The object of these experiments was, by diminishing the amount of kidney substance, to observe whether the resulting phenomena were due to a

deficiency in the excretory function of the kidney. The general result of these observations was as follows :—The removal of a portion of one kidney is not followed by any permanent after-effects, except in the case of the flow of urinary water. The removal of a portion of both kidneys produces the same excessive flow to a greater amount. The removal of a portion of one kidney and the whole of the other, again, is followed by the same effect, provided the quantity of kidney left amounts to not less than one-third of the previous total kidney volume. The removal of a portion of one kidney and of the whole of the other is followed by death, if the amount left is, approximately, no more than one-fourth of the total normal kidney weight. The period of survival after this last operation is very short—rarely more than three weeks, sometimes as short as one week. In this last series of cases, not only is the quantity of urine greatly increased, but there is also an increased excretion of urea, absolute or relative ; by the former is meant that the actual amounts excreted are greater than those previously excreted on a full diet in health. By the term “relative increase” is meant a condition in which the excretion of urea remains at the height at which it existed previously on a full diet, notwithstanding that no food is taken subsequently to the operation. In other words, if the animal refuse food, as sometimes is the case, the amount of urea excreted equals that previously excreted on a full diet; whereas, if the animal eat, the amount of urea excreted is increased. This increased excretion of urea is accompanied by great wasting, especially of the muscles, and great consequent weakness. The marasmus is accompanied by a great fall of the body temperature. The blood and tissues contain a large excess of urea and other nitrogenous extractives at a time when the increased excretion of urea is in full swing. When the animal is moribund the increased excretion of urea and urine diminishes. I think it is clear from these observations that the removal of very large quantities of kidney substance—that is, over three-quarters of the total kidney weight—is followed by a disordered metabolism of such a character that the production of urea is increased ; and that the increased urea and nitrogenous extractives present in the blood and tissues are dependent on this increased production, and are in no way caused by any deficiency in the excretory activity of the kidney.

It is most remarkable to see how these fragments of kidney will excrete quantities of urine and urea far greater than those normally excreted from two intact kidneys. The disordered metabolism produced by these extensive partial nephrectomies is in no way due to a disturbance of the nervous system produced by mutilation, since the division of the renal plexus has no influence in moderating or increasing the severity of the effects, and the phenomena are dependent entirely on the quantity of kidney substance removed at the operation, and not on the mutilation produced in removing it. Thus a greater quantity of kidney is removed by excising a wedge from one kidney, and subsequently removing the whole of the second kidney, than by removing a wedge from each kidney ; yet the mutilation and severity of the operation are far greater in the

latter case than in the former. The latter operation is never followed by an increased urea excretion ; the former may be if the quantity of kidney removed is some three-fourths of the total kidney weight. Recent experiments have suggested the increased excretion of urea is really due to inanition (Bainbridge and Beddard). My observations point to the existence of another function of the kidney apart from its excretory function ; since the latter is, at any rate, not abrogated by the procedures, whereas the metabolism of the body is very seriously deranged. Whether this is dependent on the existence of an internal secretion I am not prepared to say. Dogs that have had bilateral nephrectomy performed die sooner than those whose ureters have been ligatured ; and if renal juice or normal serum be injected into the nephrectomised animals, they live as long as or longer than those in which the ureters have been ligatured (Ascoli). It has therefore been supposed that uraemia is due to lack of an internal secretion of the kidneys, but the supposition lacks experimental proof as yet (Vitzou, and Chatin and Guinard). Finally, whether the kidney possess an internal secretion or not, it is clear, I think, that the diminution in the amount of the kidney substance available produces a widespread disturbance of the general metabolism, in no way dependent upon the impairment of its functions as an excretory organ.

THE GENERAL PATHOLOGY OF RENAL DISEASE.—The pathology of diseases of the kidney may be divided into two series of phenomena : first, the pathological results of diseases of these organs ; and, secondly, the mode of production of the diseases themselves.

Diseases involving the kidneys tend to produce one or more of the following pathological defects :—

1. Alterations in the composition of the urine ; 2, oedema ; 3, uraemia ; 4, cardiovascular changes ; 5, marasmus and anaemia ; and 6, liability to infective or so-called secondary inflammations.

1. Alterations in the Urine.—The normal flow of urine depends upon the activity of the glomerular epithelium, and on the rate of the blood-flow through the vessels. The urinary flow is diminished as the result of morbid conditions affecting one or more of the following mechanisms :—

(i.) *Circulatory Changes in the Kidney.*—(a) *The Direct Action of various Substances on the Renal Vessels.*—Substances acting on the renal blood-vessels may bring about a diminution in the quantity of urine, or even actual suppression, by causing vascular constriction. Frequently this constriction, even if extreme in amount, is followed by dilatation, depending in many cases upon damage to the vessel wall by the constricting substance, as by turpentine. Many substances which in certain doses cause constriction of the renal vessels, in other doses cause dilatation and diuresis ; citrate of caffeine is a striking example of this contrast. Further, substances like caffeine, which produce a double effect—constriction followed by dilatation—if given experimentally in rapidly repeated doses cause constriction only, and even complete suppression.

This action of substances on the renal vessels is a direct one, as shewn by the fact that division of the renal plexus has little effect on the phenomena ; and, further, that the characteristic effects can be produced in a kidney, excised from the body, through which an artificial circulation is maintained.

(b) *Indirect or Reflex Effects on the Renal Vessels produced through the Nervous System.*—Constriction of the renal blood-vessels produced by reflex excitation is not so likely to lead to diminution or suppression of the urinary flow as direct excitation ; since on reflex excitation the local effect is liable to be accompanied by a general constriction, and thus the flow through the kidney is not diminished to the same extent. It must be remembered, however, that substances acting directly on the blood-vessels have not, as far as we know, any special action on the renal vessels, and therefore, to a certain extent, the effects produced in both conditions will be similar.

Although constriction of the kidney is readily brought about by reflex excitation of the sensory nerves, it is doubtful whether complete suppression, lasting for any length of time, can be produced in this way. Stimulation of the central ends of the lower dorsal posterior roots produces reflex dilatation of the kidney, along with a general constriction.

(ii.) *Epithelial Changes.*—(a) *The Changes produced as a Result of the above Circulatory Changes.*—Interference with the renal circulation, whether by the production of constriction or dilatation, is followed very quickly by changes in the renal epithelium ; and these are undoubtedly largely responsible not only for variations in the amount of the urine, but also for alterations in its composition.

(b) *Direct Toxic Action of various Substances on the Epithelium.*—In many microbic diseases, more especially in diphtheria, anuria is not uncommon ; and often in fatal cases there are no signs of any very profound lesions of the vessels of the kidney. It is probable that in these cases suppression is brought about by the action of the morbid poisons on the epithelial elements of the kidney. This is in striking contrast to the suppression seen in acute nephritis and scarlet fever, in which the changes in the blood-vessels and circulation are very well marked.

(c) *The Action of the Nervous System directly on the Kidney Cells and on the Blood-vessels.*—This action must, at the present time, be considered purely hypothetical ; yet a number of cases of complete suppression arise as a result of reflex excitation of some part of the nervous system. This suppression may last for days ; and it is difficult to suppose that it depends entirely on reflex effects on the blood-vessels, since, as mentioned above, although it is possible, experimentally, to cause diminution in the flow of urine by the reflex stimulation of nerves, yet it is difficult to arrest the flow completely for any length of time.

An increased flow of urine is described in the section on "Urine" as a characteristic phenomenon in many diseases (p. 533). In some, as in diabetes mellitus, the mechanism is comparatively simple, inasmuch as the increased flow probably depends closely on the presence of the sugar,

which is a powerful diuretic ; it is not entirely due to this, however, as the increased flow may sometimes persist when the sugar is largely diminished. The kidneys in diabetes mellitus are usually considerably hypertrophied. In cirrhosis of the kidney the mechanism is by no means so clear. The increased flow here has usually been supposed to be dependent on the heightened arterial pressure increasing the rate of flow through the remaining kidney substance. The increased flow cannot very well be due simply to increased blood-pressure favouring filtration, inasmuch as, physiologically, the flow of the amount of urine is not dependent upon the absolute blood-pressure in the renal vessels, but upon the rate of flow through the renal vessels.

The increase seen in renal cirrhosis is somewhat similar to the increase seen after the experimental removal of portions of the kidney ; and it may perhaps be dependent rather upon the diminution in the available kidney substance than upon the increased blood-pressure. It is possible that the increase in the amount of urine may, to a certain extent, be an indication of the degree of destruction of the kidney substance. It is certainly remarkable how great are the quantities of dilute urine sometimes passed by kidneys with very advanced and general destructive and fibroid changes, a change so widespread and extensive that but little kidney structure may remain. In amyloid disease the increased flow is supposed to depend upon the increased permeability of the glomerular tuft. In chronic nephritis, in which the amount of interstitial change is frequently considerable, the flow is also increased ; and here the cardiovascular changes are often by no means so well marked as in cases of so-called granular kidney. It is difficult to say whether in these cases the increased flow is dependent simply on the increased blood-pressure, or whether here also it is related to the destruction of the kidney substance. In chronic nephritis with dropsy the subsidence of the dropsy is always associated with an increased flow of urine. In considering the polyuria of patients with chronic nephritis von Noorden lays great stress on the abnormal thirst of such patients. Left to themselves they drink copiously ; as a natural consequence their urine is copious and of low molecular concentration and specific gravity. In some the kidneys are no longer able to excrete a urine of normal specific gravity, but this is by no means always the case, and in patients with chronic renal disease the power to excrete a urine of normal molecular concentration is still present, though rarely exercised.

The other abnormalities of the urine in renal disease are considered in the section "Urine."

2. **Dropsy.**—(See article on "Oedema," p. 513 for pathology, and pp. 600, 613 for the clinical features.)

3. **Uraemia.**—The name *uraemia* is used for a group of symptoms arising during the course of many renal diseases ; always grave, not infrequently fatal, and dependent mainly, but not entirely, upon derangement of the functions of the nervous system. In this way the *uraemia* of renal disease resembles the *cholaemia* of hepatic disease.

Uraemia, more or less severe, may occur in almost all diseases of the kidney; thus it is seen in congestion—active or passive; in nephritis, especially in Bright's disease; in renal cirrhosis; in waxy kidney; in tuberculous, calculous, and cystic diseases; in hydronephrosis, and in consecutive nephritis. Furthermore, patients may sometimes succumb to uraemia with complete suppression, and with but few signs of serious disease of the kidneys. This is sometimes seen after severe injuries to sundry parts of the body, or after operative procedures on the kidney or urinary tract.

Fatal uraemia usually occurs either late in the course of chronic renal disease, or else during the course of acute nephritis very violent and severe in degree. Some of the most remarkable forms of uraemia, however, occur suddenly; either in the midst of apparently robust health, or else when the symptoms of some chronic renal disease have existed for some time, but, owing to their apparently trivial character, have been either overlooked or neglected. The uraemia accompanying fatal calculous suppression, and the uraemia of the granular or cirrhotic kidney, are instances of the latter; the uraemia of scarlatinal nephritis, of chronic Bright's disease, and of waxy kidney are instances of the former.

Uraemia may be classified clinically, according to its mode of onset or according to the nature of the most striking symptoms produced; thus, uraemia may be sudden in its onset and rapid in its course, or it may be gradual in its onset and slow and persistent in its course; the former is characterised as acute, and the latter as chronic. Some cases, however, are very rapid indeed in their progress. It is advisable, therefore, to divide the acute cases into two groups, and thus to recognise three groups in all—the fulminating, the acute, and the chronic. If uraemia be divided according to the character of the symptoms produced, two great groups can be recognised: (a) the nervous type; (b) the gastro-intestinal type. In the former the main symptoms point to disturbance of the nervous system, such as delirium, coma, convulsions; in the latter the principal symptoms point to disturbance of the gastro-intestinal functions, such as nausea, vomiting, and diarrhoea. The gastro-intestinal group corresponds fairly well with the chronic or subacute variety of uraemia; the nervous group with the fulminating or acute varieties. This classification, however, is artificial, since many symptoms in the gastro-intestinal form are probably dependent on the action of poisons on the nervous system. The symptoms in the gastro-intestinal form are remarkably constant: nausea, intense and persistent vomiting, hiccup, and frequently, but not invariably, diarrhoea. After the persistence of these symptoms for days, weeks, or months, according to their severity, certain nervous symptoms ensue; such as cramps in the legs, muscular twitchings, contraction of the pupil, occasional and inconstant delirium, and gradually increasing dyspnoea—possibly of the Cheyne-Stokes variety, but more particularly characterised by its peculiar hissing quality. The delirium gradually gives way to drowsiness and coma, and

the patient dies from failure of respiration, sometimes gradually, sometimes with remarkable suddenness.

The symptoms in the fulminating and acute forms are much more protean in their manifestations, and may be divided as follows:—

(1) *The Eclamptic or Epileptiform Type.*—In this form, with or without previous warning, the patient is seized with an epileptic seizure, usually beginning, like other forms of epileptic seizures, with movements involving the small muscles, then spreading rapidly to the whole body. The fits are frequently repeated, and may be of great severity, the patient passing into a condition allied to the status epilepticus. There is usually unconsciousness, which, however, is not always absolutely complete, and the body temperature falls. The pupils are contracted and the knee-jerks exaggerated; and often—if the fits are very frequent and severe—the body temperature rises considerably, and there may even be hyperpyrexia without the presence of any gross inflammatory lesions in the lungs, or elsewhere, to account for the height of the fever. This type of uraemia in its pure form is not common, except in eclampsia; but epileptiform seizures of a similar type occur in other forms of uraemia. Sudden seizures of very great violence may occur in cases of granular kidney associated with high blood-pressure. These epileptiform attacks are most prone to occur when the arterial blood-pressure is very high, and in some instances extreme high arterial pressure may be present without extensive degeneration of the arteries. Such attacks, although very serious, are by no means always fatal if their nature is recognised and proper treatment, especially venesection, be adopted.

(2) *The Maniacal Form.*—This, also, is not a common form, but it is seen occasionally in cases of contracted kidney in young adults; sometimes in cases in which symptoms of renal disease have existed and been recognised for some time; in other more obscure forms in which the onset of violent mental symptoms has been the first indication of the underlying malady. The patient is excited, restless, noisy, and sometimes very violent; in two cases under my own observation very distinct cataleptic phenomena were present at intervals. The excitement soon gives way to drowsiness, and then to coma and other distinct uraemic symptoms.

(3) *The Dyspnoeic Form.*—Dyspnoea of a peculiar hissing character, as noted by Addison, is common in uraemia; sometimes it is almost the only sign present, even in fatal cases. Such patients are seized with a dyspnoea so intense as in some cases to suggest laryngeal obstruction, the patient sitting up and gasping for breath. The breathing is very noisy, hissing, and asthmatic in type, but there is very frequently no great lividity, and the patient is frequently conscious, and his mind clear. The dyspnoea much resembles the paroxysmal attacks seen in leukaemia; more frequently, however, the dyspnoea is only the accompaniment of other uraemic manifestations, and its peculiar hissing quality in a drowsy patient, with bleeding gums, is very characteristic of the uraemic state. Very violent paroxysms of dyspnoea, so far as I have seen, are most

marked in the acute uraemia supervening in cases of contracted kidney. The other or hissing variety is more often seen in chronic uraemia, and greatly resembles the breathing seen after the administration of excessive doses of salicylates. The respiratory rhythm in uraemia is often periodic rather than rhythmic ; and the form usually assumed is that known as Cheyne-Stokes breathing. The periodicity affects not only the respiratory rhythm, but other functions also ; and in a well-marked case the following phenomena occur : with the waxing and waning of the respiratory rhythm the pulse-rate is altered in such a way that the rate is quickened with the noisy breathing, and slows down again during the period of apnoea ; the periodic variations in the pulse-rate are not quite synchronous with the periods of respiratory rhythm ; there is, so to speak, some slight overlapping ; the pupil contracts and dilates, the dilatation occurring with the noisy breathing or just preceding it, and, further, during the period of noisy breathing the patient is restless, subject to irregular muscular movements until during the apnoeic period he gives way to complete temporary coma.

These phenomena shew that Cheyne-Stokes breathing is something more than a mere periodicity of the rhythm of the respiratory centre, and that many other functions of the nervous system are simultaneously affected. In some cases in which Cheyne-Stokes breathing is seen, the patient is not completely unconscious, and a waxing and waning of consciousness may be observed ; but this is a rare phenomenon in comparison with the others described above. Cheyne-Stokes breathing is more common in chronic uraemia and in the acute exacerbations of chronic uraemia than in acute and fulminating cases.

(4) *The Comatose Form.*—This is the commonest form of uraemia ; and in this form the patient, with or without delirium, passes into a state of drowsiness deepening into coma. Sometimes the coma is preceded by cramps and twitchings, and the latter are usually to be observed, especially in the forearms, during the progress of the case. At other times the coma is preceded by gastro-intestinal phenomena, especially by nausea and vomiting ; sometimes by intense headache or loss of vision, partial or complete, and there is always a considerable fall in the body temperature.

Some of the most acute cases of uraemia occur, however, quite suddenly, and without any marked prodromal symptoms ; such patients, after a short period of delirium, or even without, suddenly become drowsy and rapidly comatose, with contracted pupils, excessive knee-jerks, and subnormal temperature. During this coma epileptiform fits may occur, but these are by no means an invariable accompaniment of uraemia. In all forms of uraemia the tongue is apt to become dry, brown, and cracked.

Other rarer forms of uraemia may be described, and more especially the following :—

(5) *The Paralytic Form.*—In this remarkable condition a hemiplegia, even a monoplegia may occur suddenly without any gross lesion to account for the paralysis being found after death.

(6) A form in which persistent *inability to sleep* is the most marked phenomenon, associated with twitching, cramp, and hiccup ; but the mind remains clear and there is no coma : death occurs rather suddenly from respiratory failure.

(7) *Latent Uraemia*.—This is probably the most remarkable of all ; it is seen more especially as the result of complete obstructive suppression of urine, and has been fully described by Sir William Roberts. It is seen when both ureters are obstructed simultaneously ; or, more commonly, where bilateral calculous disease has led to the complete destruction of one kidney in the past, and then the ureter of the sole remaining kidney becomes suddenly obstructed, and no urine is passed. Sometimes a very small quantity of urine is pent up in the renal pelvis behind the obstruction, and it is not common in a case of complete suppression to find at the necropsy no urine pent up in this situation. The symptoms in this class are remarkable for their slight intensity, and for this reason the term latent uraemia is perhaps applicable to such cases. Such patients will live for seven, ten, or even fourteen days without expelling any urine. They remain conscious almost to the end ; and all the so-called uraemic symptoms are conspicuous by their absence. The symptoms are described in the account of calculous anuria (p. 702). This symptom-group has usually been said to occur in cases of calculous suppression only ; but I have seen a precisely similar state where, owing to endarteritis and thrombosis of the interlobular arteries of both kidneys, the renal secretion was practically arrested, and the patient lived for seven days without secreting any urine. The symptoms presented by this patient were those described by Sir William Roberts as characteristic of double calculous suppression.

The difference between the group of symptoms seen in calculous suppression and the ordinary forms of uraemia is very great, and has considerable bearing on the interpretation of uraemia.

Attempts to explain the nervous disturbances in uraemia have hitherto been made on what may be called the mechanical and the chemical bases. According to one school, the results are due to the excitation or paralysis of the nerve structures by the changed physical conditions brought about by cerebral oedema or cerebral anaemia ; according to the other, the results are due to the action on the nerve-cells of one or more poisons circulating in the blood-stream.

Cerebral oedema is seen, no doubt, in cases of fatal uraemia unassociated with general dropsy, but the general feeling is that it is rather the result of atrophy of the cerebral convolutions than an active condition. Cerebral oedema was invoked to explain uraemia, as it affords a possibility of accounting for localised uraemic disturbances ; modern knowledge, however, certainly shews that a poison circulating in the general blood-stream may pick out but one portion of the nervous system, or even produce a lesion on one side of the body only. Lead and arsenic afford numerous instances of such actions. Absinthe gives rise to toxic epilepsy due to cortical irritation. Both may cause symmetrical

peripheral neuritis ; but what is more remarkable is that either of them may cause a patch of focal myelitis. Arsenic not infrequently causes herpes, which in all probability is dependent on a nerve lesion, and is generally unilateral in its distribution. Further, one and the same poison may produce opposite effects at different times or in different cases. Thus, lead poisoning may cause convulsions or palsy. That uraemic manifestations are sometimes localised, and are not always uniform, does not militate in any way against the view that their source is a toxic one.

An active inflammatory oedema is as familiar to pathologists as a dropsical cerebral oedema is unfamiliar ; but there is no evidence of the existence of such a condition in uraemia.

Cerebral anaemia will undoubtedly produce many of the effects so often seen in uraemia. For instance, convulsions, epileptiform fits, Cheyne-Stokes breathing can all be brought about experimentally by ligature of one or more of the cerebral arteries ; and it is possible that cerebral anaemia may be responsible for some of the phenomena seen in uraemia. The difficulties in the way of this view are that modern investigation shews no evidence of any well-developed vasomotor mechanism supplying the cerebral vessels ; and further, that the state of the cerebral vessels is mainly dependent on the state of the vessels at large. Contraction of the vessels of the body leads to distension of the cerebral vessels, and cerebral anaemia is more readily brought about by causing dilatation of the vessels of the body than by causing active constriction of the vessels of the brain. In fact, there is no method by which active constriction of the cerebral vessels can be brought about experimentally. It is probable that even if the blood were to contain a substance capable of constricting the cerebral vessels, the vascular constriction and the heightened blood-pressure produced by its simultaneous action on the other vessels of the body would overpower the local cerebral effect.

One of the principal reasons for looking upon uraemia as dependent on physical causes is that uraemia is so often associated with a granular or fibroid kidney. This condition is one in which, owing to the existence of extensive lesions in the vascular system producing great thickening and narrowing of the arteries, it is possible that anaemia of the tissues might be produced. It has also been shewn that in some cases the uraemic convulsions are controlled by lumbar puncture, especially in cases in which the fluid spurted from the cannula, and was therefore at high pressure (Willson). Uraemia in granular kidney is common when the blood-pressure is high ; and, notwithstanding the thickening in the arteries, the blood-pressure in this disease frequently varies, and a temporary increase in blood-pressure and uraemic manifestations have long been known to be associated. Further, venesection, or a spontaneous haemorrhage, such as epistaxis, will frequently relieve at the same time both the increased tension and the uraemia. These are the principal reasons that led Traube to form his celebrated hypothesis of

cerebral oedema and anaemia. For the reasons mentioned above this hypothesis cannot now be accepted, although there can be no doubt, as just pointed out, that high blood-pressure is frequently associated with uraemia, and especially with the epileptiform seizures that occur in cases of granular kidney. High tension, and even extensive arterial disease, are not necessarily associated with extensive disease of the cerebral vessels; thickening of their walls cannot be inferred by the examination of the pulse, nor by the absence of marked high tension. It is not uncommon to see the cerebral vessels extensively thickened without obvious general disease of the other vessels; and on the other hand, extensive disease of the vessels of the body may exist with comparatively little disease of the cerebral vessels or even none. Further, high blood-pressure, even in an extreme degree, may be present and be associated with epileptiform seizures, and yet the blood-vessels may not be extensively degenerated.

For these reasons the majority of observers look upon uraemia as dependent on the presence of toxic material in the blood, and the excitation of the nervous structures by this poison. Unfortunately, however, no such poison has hitherto been separated and identified, and the great variety of uraemic manifestations has suggested the possibility that more than one toxic body is present.

The toxic substance may appear in the blood under one or more of the following conditions: (i.) that a body that ought to be and normally is excreted, is retained; (ii.) the abnormal decomposition in the blood or tissues of such a body; (iii.) the formation of abnormal products of metabolism by the tissues.

(i.) The first is the simplest explanation of uraemia, and one very generally accepted. In many cases of subacute and chronic uraemia, and in the violent uraemia seen in acute nephritis, the quantity of urine excreted is often very small, and examination of the blood shews the presence of greatly increased quantities of nitrogenous extractives. The amount of urea in the blood may be twenty times greater than normal; and although this substance may not be directly answerable for the effects produced, its presence in these large amounts serves as an index to the amounts of other and perhaps unknown bodies, possessing toxic actions, which may be present in large quantities. Bouchard has insisted strongly on the fact that the urine normally is toxic, that its toxicity depends on a number of substances, more especially salts, pigmentary matters, and certain unknown constituents, and that the nitrogenous extractives present in the urine, and more especially the urea, possess but little poisonous action. He conducted a series of observations shewing that a certain quantity of urine injected into the circulation is fatal; in some cases death was preceded by convulsions, in others by coma; in nearly all contraction of the pupil and failure of respiration were marked symptoms. By comparing the amount of urine injected with the weight of the animal, he established what he called urotoxic equivalents, and found, as a mean of a large series of observations, that 25 to 75 c.c. of

urine per kilogram of body weight of the animals used (rabbit) were fatal. Ligature of the ureters and double complete nephrectomy is usually fatal on the third day, and some of Bouchard's observations tend to shew that the amount of urine excreted in three days is toxic if injected at any one time. Bouchard, however, stated that the urine in many cases of uraemia loses its toxicity largely or in part; and he deduced from this that the toxic principles are retained, and produce the well-known symptoms.

The principal difficulties in the way of the acceptance of this view are, in the first place, that when suppression of urine occurs in the human subject, as in cases of calculous anuria, the symptoms produced are very peculiar, and not those that are usually considered characteristic of uraemia. Secondly, in a very large number of cases of acute uraemia with granular cirrhotic kidney there is often no evidence of any considerable suppression of urine. Such patients often pass very considerable quantities of urine, containing less urea, it is true, than normal, but not necessarily less than many patients, suffering from other diseases and taking but little food, would pass. In my experience it has not been uncommon to find patients dying of acute uraemia with granular kidneys, excreting as much as 10 to 12 grams of urea in the last twenty-four hours of life. Moreover, as such patients are usually unconscious, it is impossible to collect all the urine; hence, these quantities do not really represent the total amount excreted. Many patients suffering from other diseases with no complication of the kidneys, and even healthy patients, often do not pass more than 10 to 15 grams of urea per diem. Such may be the case in patients who have undergone ovariotomy and have been kept for twenty-four hours without food.

Patients dying from acute uraemia often take little or no food for many days, and still more frequently reject what they do take; moreover, the urine is often highly albuminous, and the protein thus excreted represents a nutritive loss; hence it is unreasonable to expect such patients to pass quantities of urea at all comparable to those seen in health, and the mere fact that the excretion may be, comparatively speaking, low, does not prove that the kidney is unable to excrete the nitrogenous extractives.

The blood in cases of ordinary uraemia arising from renal disease contains a large excess of nitrogenous extractives, frequently as much as twenty times the normal. Again, the blood of patients who have granular kidneys, and the blood and dropsical exudations of patients with chronic Bright's disease, contain very considerable quantities of urea and other nitrogenous extractives at a time when the patient is free from obvious uraemic symptoms. The blood normally contains, approximately, 0·015 per cent of urea. In renal disease without uraemia this may rise to 0·15 per cent, and this at a time when the patient is excreting quantities of urea within the limits of health. With the supervention of acute uraemia the quantity may rise in the blood to 0·4 or even 0·5 per cent.

No experimenter has been able to reproduce all the symptoms of uraemia, either by the injection of urea or of other nitrogenous extractives; and although the blood, in cases of ordinary uraemia, contains this large excess of nitrogenous extractives, such is not the case in eclampsia. Even in fatal cases of eclampsia the blood does not contain quantities at all comparable to those seen either in uraemia or in cases of calculous suppression, the highest percentage observed by myself being 0·06 per cent.

Retention undoubtedly affords the simplest explanation of the presence of these large amounts of extractives in the blood; but I think there can be no doubt that these extractives are present in increased amount at a time when there is no evidence of a greatly diminished nitrogenous output; and further, as mentioned above, the urine contains quite appreciable quantities of extractives, even in the last twenty-four hours of life, since on the whole it is exceptional to see complete suppression of urine in cases of acute uraemia in the granular kidney.

(ii.) Seeing all these difficulties in the way of explaining uraemia as dependent simply on the retention of some normal constituents of the urine, many observers have fallen back on the view that, owing to the diminished excretory activity of the kidney, the retained urinary constituents undergo decomposition, either in the blood at large or in the alimentary canal. It has been suggested that the urea decomposes into carbonate of ammonia, and that the toxic phenomena of uraemia are due to the presence of this body. Carbonate of ammonia, when injected into the circulation, will undoubtedly produce many symptoms characteristic of uraemia, such as convulsions and dyspnoea. Many observers, however, have failed to detect ammonia in the blood in fatal cases, and for this reason the suggestion has not received any large measure of support. Inasmuch as there are these serious difficulties in the way of the retention and decomposition hypotheses of uraemia, Perls and Schottin suggested long ago that the toxic substances in uraemia might be derived from the products of abnormal metabolism. There are some facts in favour of this view. In the first place, the typical phenomena of uraemia are not those seen as the result of simple suppression. Again, in cases of uraemia, the quantities of nitrogenous extractives in the blood, and more especially in the tissues, such as the muscles, are far greater in percentage amount than in cases of complete calculous anuria. This suggests that the quantities of these bodies are too great to be accounted for by retention.

(iii.) My experiments, mentioned above, have shewn that when the available kidney substance is greatly reduced in amount, the excretory functions of the kidney are not only not seriously interfered with, but that the excretion is actually increased; and that, notwithstanding this, the blood and tissues of the animals contain very large quantities of urea and other nitrogenous extractives. In the experimental cases these nitrogenous extractives must have arisen from increased tissue disintegra-

tion, for no retention occurred, but a positive increased excretion of urinary water and urea ; and these experiments suggest very strongly that when the available kidney substance is diminished beyond a certain amount—roughly speaking, one quarter of the total kidney weight—the protein tissues undergo rapid disintegration with the formation of abnormal quantities of extractives. These experiments, then, lend some support to this view of uraemia, although the classical symptoms of uraemia appeared in none of the animals. According to Ascoli, even the total toxic effect produced by all known urinary substances is insufficient to account for the symptoms of uraemia. It is possible, however, that the retained substances accumulate, and so are able to act more powerfully than at first sight would appear probable. It is also probable (von Noorden) that, whereas these retained substances have always been sought for in the blood, they have special affinities for certain cells in the body, just as morphine or the toxin of tetanus combine preferentially with cells in the central nervous system. The question of the localisation of these extractives in the various tissues therefore requires further investigation before it can be definitely decided that they are not the cause of uraemia.

4. Cardiovascular Changes.—Widespread changes in the cardiovascular system are common in renal disease, and more especially in certain forms of it, such as renal cirrhosis and chronic Bright's disease. The pathological changes produced in renal disease involve the heart and the large and small arteries ; the former becomes hypertrophied ; the changes in the arteries, however, are not so simple. In many cases the large arteries lose their elasticity, but this is by no means a constant change, and in very far advanced renal disease the large arteries may still be very elastic. The inner coat of the larger arteries frequently presents atheromatous changes, but these again are not an invariable accompaniment of renal disease. The medium-sized and small arteries have their coats very much thickened, and this thickening affects mainly the internal coats. In the small arteries the changes are on the whole most evident in the internal coat. The middle coat of the thickened arteries may shew an increase in the amount of muscular tissue, and this in some cases is exceedingly well marked. In others, apparently, the increase in this coat is largely dependent on fibroid change ; but it is probable, although questioned by some, that, in many cases of renal disease, there is a true hypertrophy of the muscular coat. The thickening of the internal coat is largely dependent on the formation of loose fibrous tissue in the deeper layers, so that the subendothelial tissue is greatly increased in thickness ; this increase is not always uniformly distributed, and not uncommonly the endothelium is thickened also, but this is not so frequent as the thickening in the subendothelial layers. The thickening of the inner coat decreases the lumen of the vessel very considerably, and the thickening of the middle coat—especially when fibroid—is sufficient to be readily recognisable by the finger in such an artery as the radial.

The arterial changes are frequently widespread, but they are not

uniformly distributed, and they are most marked in the vessels of the kidney itself: in some cases, perhaps, they are restricted to these vessels.

In addition to the above changes in the arteries miliary aneurysms are commonly present, especially in the cerebral vessels. These miliary aneurysms, it is well known, affect more particularly the small arteries, and they are frequently present in enormous numbers. The fibrotic kidney and certain forms of chronic Bright's disease are the renal lesions most frequently associated with the presence of miliary aneurysms, and hence these are the renal diseases in which cerebral haemorrhage is most prone to occur.

The aneurysms of large vessels, due to atheromatous changes in their walls, are by no means necessarily associated with renal disease; although the high arterial blood-pressure in renal disease is usually held to be one of the remoter causes of aneurysm.

Hyaline changes in the capillaries, especially in those of the glomeruli, are commonly associated with the cardiovascular changes described above.

The cardiac hypertrophy of renal disease is usually moderate in amount, and unless there be coexisting valvular defects it does not attain the degree which is seen in the latter condition. The hypertrophy of renal disease affects the left side of the heart mainly yet not exclusively; but unquestionably the hypertrophy of valvular disease affects the right side of the heart more than the hypertrophy of renal disease does. Still in the latter case, if the enlargement of the heart be considerable, the right side shares in it to a slight extent.

These widespread lesions of the vascular system are most extensive in certain cases of renal cirrhosis; more especially in that condition known as red granular kidney, or raspberry kidney, which occurs in middle-aged persons; and the greater and more widespread the arterial disease the greater the cardiac hypertrophy. The vascular lesions are also fairly well marked in cases of chronic Bright's disease, where the size of the kidney may be variable, sometimes a little larger than the normal, sometimes a little smaller, but where there is considerable fibroid change in the kidney. These cases often occur in the comparatively young, and the arterial thickening and cardiac hypertrophy may occasionally in these cases reach the degree seen in the granular kidney. Such patients may succumb to cerebral haemorrhage. On the other hand, cases of chronic Bright's disease with the kidneys shrunken and fibroid, the capsule thickened and leaving a granular surface on stripping, may exist with comparatively little hypertrophy or arterial change except in the renal vessels. It is not very uncommon to see cases of death from uraemia with the kidneys weighing about three ounces apiece, and very granular on the surface; but the stripping of the capsule does not tear the cortical substance, and in such cases the heart may not be appreciably enlarged, and the arteries generally are not thickened to any great extent.

The amyloid kidney is not associated with any profound arterial changes except those necessarily associated with the presence of waxy disease in the body; and the heart in these cases is not hypertrophied.

Extensive destruction of the kidney substance by hydronephrosis, even if double, is not necessarily associated with profound cardiovascular changes. On the other hand, in some cases, and more especially perhaps in the double hydronephrosis seen in young persons and probably dependent on congenital abnormalities, the cardiac hypertrophy is a well-marked phenomenon. Cases of partial hydronephrosis associated with fibroid change in the rest of the kidney are not uncommonly seen ; the upper or anterior half of the kidney is little more than a sac, and the available kidney substance is spread out in the posterior or lower portion. In such cases cardiac hypertrophy is often a marked feature.

Acute and subacute Bright's disease lead very rapidly to the production of high arterial blood-pressure ; and cardiac hypertrophy and arterial changes, if the malady last so long as six weeks, may be observed ; that is to say, in this time obvious physical signs pointing to the existence of hypertrophy can be detected. Many cases of chronic Bright's disease associated with dropsy exist for long periods without leading to the marked cardiovascular changes associated with high pressure.

From the above facts the following deductions may, perhaps, be possible. High arterial blood-pressure is a frequent accompaniment of renal disease, and more especially of the condition known as the granular kidney occurring in middle-aged persons. It is also well marked in the contracted kidney occurring in the young, as a sequel to acute or chronic nephritis ; but it is not an invariable accompaniment of these conditions. Finally, extensive destruction of both kidneys may take place without necessarily producing the graver widespread vascular lesions associated with high blood-pressure.

The explanation of the cardiovascular changes accompanying renal disease, and especially evident in certain forms of it, is by no means simple. It is usually supposed that a condition of what has been called "functional high tension" precedes the anatomical changes described above ; that is to say, the blood-pressure is increased as a result of an increased activity of the vasomotor system with consequent contraction of the arteries ; the excitation of the vasomotor mechanism being produced by the circulation in the blood of some material capable of exciting it. In favour of this opinion is the undoubted fact that the pulse in renal disease frequently shews the characteristic features of high pressure, when there may be no clinical evidence of anatomical changes in the vessel. This is more especially true of acute renal disease, but it is also true of some instances of chronic renal disease. Further, the degree of pressure is variable, and a smart haemorrhage, say, from the nose, will often relieve it greatly. There is, however, no evidence to identify the substance or substances that cause this functional increased activity of the vasomotor system, and some authors have supposed that the cardiac hypertrophy is not the result of the vascular obstruction, but actually the cause of it ; and they consider that the circulation in the blood of increased amounts of nitrogenous metabolites, such as urea and its allies, causes an increase in the force of the heart-beat, and that in this manner

the vessels are exposed to an increased strain, the results of which are the thickening and other changes observed in the arteries.

At any rate, the injection of urea temporarily increases the blood-pressure, yet this substance has certainly no influence in causing arterial constriction ; if, therefore, the high tension of renal disease depends on the presence of increased amounts of nitrogenous extractives in the blood, the effects may be produced by a primary action on the heart.

Again, it has been suggested that the high tension of renal disease is brought about by an attempt to maintain an efficient rate of blood-flow through the remaining kidney substance ; now inasmuch as this area is greatly diminished in extent, the flow can only be maintained at a normal rate by an increase in the general blood-pressure produced by constriction of other vascular areas causing an increased rate of flow through the remains of the kidney.

Speaking broadly, the high pressure in renal disease certainly varies inversely as the extent of kidney substance present ; and it reaches its maximum in renal cirrhosis. Experimentally, I was unable to reproduce the characteristic lesions seen in the arterial degeneration of renal disease as the result of the removal of large quantities of kidney, but the blood-pressure was apparently raised.

In many cases of renal cirrhosis it is probable that the widespread arterial changes are primary, and that the lesions in the kidney, especially those in the epithelium, are secondary to the vascular lesion ; in other words, the interference with the circulation through the kidney leads to the decay of the higher renal elements, and thus the overgrowth of fibrous tissue subsequently found in the kidney is secondary to this, and not a primary lesion. (*Vide* art. "Arteriosclerosis" in Vol. VI.)

Considerable lesions of the smaller vessels of the kidney, with great thickening of their walls and a narrowing of their lumen, may, however, exist without the presence of any fibrosis.

5. Marasmus and Anaemia.—Renal disease frequently produces well-marked anaemia, and also great wasting. The extent of the latter may be very largely concealed by the presence of dropsy. In some renal diseases emaciation is one of the early symptoms. The wasting of renal diseases is dependent on many causes. In the first place, such patients have an impaired nutrition, dependent on serious disorders of the gastro-intestinal tract : the appetite is poor ; nausea, vomiting, and diarrhoea are common. The quantities of albumin lost in the urine are often considerable, especially in chronic Bright's disease ; and in this way the nutrition of the patient is still further affected, since such patients frequently pass in the urine one-quarter or one-third of the total protein ingested. Wasting, however, may be a marked feature of renal cirrhosis, in which the disturbance of the gastro-intestinal functions may be slight, and in which the albuminuria is always slight ; the emaciation in these cases resembles the rapid wasting that is seen experimentally when large quantities of the kidney substance are removed, a condition which I have shewn—at any rate experimentally—to be dependent on an

increased disintegration of the protein tissues, more especially of the muscles.

Anaemia in renal disease is present in almost all cases to a greater or less extent; but it is specially well marked in chronic Bright's disease associated with dropsy. Such patients are exceedingly pale. Many patients with granular kidney, especially in the form of it seen in young persons, are also frequently very pale; and the anaemia of renal disease, like the wasting, is often of complex origin. Many patients suffer from profuse haemorrhages, specially from the nose or from the urinary tract; and in the latter case, if very profuse, it not improbably arises from the pelvis of the kidney. The dyspepsia and gastritis necessarily present in this disease will also tend to cause anaemia, and it is probable that the widespread disorders of nutrition also tend in this direction.

The anaemia of renal disease may be extremely severe; and many of the vascular murmurs characteristic of anaemia are very evident in cases of renal disease.

6. Secondary Inflammations (*vide p. 617*).

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NEPHRITIS

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Introduction.—There is a group of affections of the kidney in which one of the leading features is the presence of albumin in the urine. In some of these diseases the albuminuria is the most important characteristic, in others it is an accompaniment of dropsy, impairment of nutrition, anaemia, cardiovascular changes, and the toxic phenomena included under the general heading of uraemia. These affections of the kidney are of very varying degrees of severity: some are trivial, presenting few or no

symptoms and not leading to any permanent departure from health ; others are rapidly fatal ; and in a third group there is great impairment of health, often lasting for months or years and frequently terminating fatally.

The great variations in the severity of these different renal affections make their classification a matter of considerable difficulty. Further, the general effects, such as the impairment of nutrition, the presence or absence of dropsy, and the cardiovascular degeneration, do not necessarily vary in degree with the severity of the renal affection as gauged by the changes produced in the urine, and more especially by the quantity of albumin present. Some of the most serious forms of kidney disease present but a slight degree of albuminuria, and the mere presence of a large quantity of albumin does not necessarily establish the existence of grave and chronic renal disease.

The nomenclature of these affections is somewhat unsatisfactory, but the descriptive title nephritis is usually applied to most of them, although in not a few clear evidence of the existence of a pathological state akin to inflammation is wanting. The name nephritis is sometimes applied with equal readiness to the albuminuria present during the height of an acute infective process which was formerly described as febrile albuminuria, and to an inflammatory affection of the kidney of great severity such as that produced by cantharides, turpentine, or the virus of some acute diseases such as scarlet fever. In the first there is no greater disturbance of the economy than the presence of a very small quantity of albumin in the urine, whilst the second may rapidly prove fatal from complete suppression of the urinary function and the consequent production of a lethal toxæmia. These extreme conditions may be taken as illustrative of the variations in the intensity of so-called acute nephritis ; but the term nephritis is not even limited to such conditions as these, and it is often applied, especially in the form of chronic nephritis, to conditions differing widely not only in the severity of the symptoms or in the nature of the morbid lesions, but also in the course of the maladies. In some instances of renal disease the malady comes on insidiously, runs a prolonged course, and is characterised by the persistence of symptoms such as dropsy, anaemia, albuminuria. In many cases the course of such a malady, although not uniform, is ultimately unfavourable, and in this respect this form of chronic renal disease resembles the course of other chronic affections. Such a condition is appropriately described as chronic nephritis. In another group of cases after an attack of acute nephritis all the symptoms clear up with the exception, perhaps, of albuminuria of a varying degree of severity ; the dropsy may completely disappear, and the patient regains the appearance of usual health, but albumin may be present in the urine for months or even years. This class of case is also often spoken of as chronic nephritis, and the malady is regarded as the direct sequel of the acute lesion that preceded it. There is a great difference between these two groups of cases ; not only is albuminuria the sole symptom in the one, whereas in the other it is accompanied by

phenomena of a greater or less degree of severity, but there is the further and important difference that in one class of case the condition is progressive, whereas in the other it is more or less stationary. It is unsatisfactory to speak of both the classes as chronic nephritis, especially as the difference in the prognosis of the two conditions is great. The one lesion should be looked upon as accurately described as chronic nephritis; the other should rather be regarded as a lesion produced by the acute disease, but not necessarily of grave import, and possibly even non-progressive in character. Another difficulty in nomenclature arises from the confusion between the terms Bright's disease and nephritis. Many writers use these two terms synonymously and as equivalent to acute and chronic nephritis, others restrict the term Bright's disease to the chronic affection, and others again use the word nephritis when speaking of the less serious and Bright's disease when dealing with the more serious affections, both acute and chronic.

There is the further difficulty that Bright's disease is sometimes held to include lardaceous disease of the kidney and also the granular kidney. The clinical picture presented by some cases of lardaceous kidney closely resembles that seen in chronic nephritis, and, further, it is not uncommon for the lesions of chronic nephritis and those of waxy change to coexist in the same kidney. Many instances of the large white kidney, and especially those described in former years, are really examples of amyloid change. Lardaceous disease of the kidney being usually part of a widespread change affecting many organs and tissues of the body should be classified apart from nephritis and Bright's disease. There are great difficulties in classifying satisfactorily the granular kidney, inasmuch as this name is applied by different writers to a very considerable number of different renal lesions; in fact, by some to all conditions in which the fibrous tissue of the kidney is increased in amount and the surface of the organ is irregular from the unequal distribution of the fibrosis in different parts. Further, the mere adhesion of the capsule to the kidney substance depending on this formation of fibrous tissue is often regarded as sufficient evidence to classify the kidney as granular. Others limit the term to the well-known degeneration of the kidney associated with marked cardiovascular and especially arterial lesions, in which the degree of fibrosis is very considerable. Some forms of renal fibrosis doubtless date their origin from an affection of the kidney that may be described as a nephritis, acute or chronic; but a considerable number of cases of granular kidney are the result of a slow degeneration of the kidney and blood-vessels generally. Not only is this so, but there is much evidence to prove that the renal change may be the direct result of the arterial disease, and therefore merely a local manifestation of a widespread degenerative process. This form of granular kidney has no direct relation to acute or chronic nephritis, and is more accurately classified as a degeneration, and hence it is doubtful whether it should be spoken of as Bright's disease, although clinically such cases may present dropsy and albuminuria. Dropsy and albuminuria may, however, both be present without there

necessarily being nephritis or Bright's disease, as, for example, in cardiac disease with passive congestion of the kidney; and although the albuminuria in such a case no doubt depends on changes in the epithelial elements of the kidney, the condition is very different from nephritis associated with dropsey.

Thus, the organic diseases of the kidney associated with albuminuria may be classified under the heads of nephritis, fibrosis, and amyloid disease. Albuminuria, however, may exist even in considerable amount without the presence of any of these gross changes, and, further, several varieties of such albuminuria may be recognised, such as functional or physiological albuminuria, the albuminuria of passive congestion, and the albuminuria resulting from vascular lesions other than passive congestion, more especially that due to infarction. All these varieties of albuminuria are liable to be confounded with the more serious form dependent on renal degeneration, but they are especially liable to be confounded with nephritis. The albuminuria of passive congestion and of infarction is apt to be sudden in its onset, and is often marked in degree, and may be accompanied by haematuria, and thus the resemblance to some forms of nephritis is considerable. Passive congestion and infarction are especially liable to occur as complications in cardiac disease, and genuine nephritis may also develop in such patients. The so-called functional or physiological albuminuria is sometimes difficult to recognise, and may be confounded with the albuminuria of chronic renal disease, and especially with some forms of chronic Bright's disease and of granular kidney.

Nephritis is usually defined as inflammation of the kidney, although it must be admitted that many of the conditions included under this heading might be more correctly described as due to a toxic action on the renal elements. In some forms the inflammatory phenomena are well marked as gauged by the congestion of the blood-vessels of the organ and the exudation, and also by the changes in the urine, such as the presence of blood. In other instances, however, of severe nephritis the main lesion is necrosis and degeneration of the renal epithelium. It is difficult, if not impossible, to separate these two types, and they are usually both included under the heading of nephritis. In most forms of nephritis all the elements of the kidney suffer, but in varying degrees; and definite forms have been recognised as glomerular, tubular, and interstitial nephritis. It is, however, very rare for any form of nephritis to affect exclusively one only of these sets of structures. Thus, it is almost impossible for the glomerular nephritis to leave the tubules unaffected since the lesion in the glomeruli, if at all severe, will interfere with and possibly arrest the circulation in the vessels supplying the convoluted tubules, and thus a glomerular lesion is necessarily accompanied by a greater or less degree of degeneration of the tubular epithelium. The toxic agents that lead to degenerative processes in the tubular epithelium also commonly produce some effect on the epithelial structures of the glomerular chamber. Thus, a pure tubular nephritis or a pure glomerular nephritis must be a great rarity. Further, interstitial nephritis can hardly

occur to any considerable degree without producing secondary effects in the renal tubules, and hence it comes about that the descriptive title glomerular nephritis is applied to a lesion in which the glomerular lesions predominate. Similarly, the term interstitial nephritis is employed when the morbid processes are most marked in the loose connective tissue separating the renal tubules. Nephritis may be acute or chronic, and much difference of opinion has been expressed with regard to the relation of chronic nephritis to the more acute process. Some writers consider that chronic nephritis is usually the sequel of acute nephritis, whilst others believe that this is very exceptional, and that most instances of chronic nephritis are chronic from the commencement. It is often difficult to distinguish between chronic and acute nephritis because the onset of the disease is so often very insidious; further, symptoms may arise suddenly in the course of chronic and latent disease, so that many cases of chronic nephritis, often of long standing, may present acute symptoms and thus give rise to the impression that the renal lesion is acute. Again, the epithet chronic is often applied in cases in which, after an acute onset, the symptoms have persisted for a considerable time, for instance, for several months; and there can be no doubt that in a certain proportion of cases of acute nephritis, for example in that complicating scarlet fever, the renal lesion persists, and that these cases should be classed as instances of chronic renal disease dating from an acute attack. The relation of chronic to acute renal disease is, however, often less close. Thus, the acute lesion may clear up and the urine remain free from albumin for long periods, and then a recurrence of the nephritis may take place, and possibly then the albuminuria remains persistent.

But in a very large proportion of cases of chronic nephritis the onset is so insidious that no history of an acute renal affection can be obtained. This applies to all forms of chronic nephritis, not only those instances in which the lesion is mainly tubular or parenchymatous, but also to the many varieties of renal sclerosis. It is probable that chronic renal disease, especially the form in which fibrosis of the kidney is a prominent feature, may arise a long time after an attack of acute nephritis, and after an intervening period of good health between the acute disease and the manifestations of the chronic lesions. It must, however, be remembered that chronic renal disease, often of a severe type, may be present for long periods without producing symptoms of sufficient intensity to attract attention, and that in not a few cases the existence of the malady in an advanced form is discovered accidentally as the result of a routine examination of the urine.

Under the heading of etiology the factors concerned in the causation of the three main forms of nephritis will be considered. After this separate descriptions of (i.) acute nephritis; (ii.) chronic nephritis, including the forms known as the large white kidney and the contracted or small white kidney; and (iii.) of granular kidney, will be given.

Etiology.—Nephritis has been attributed to a large number of

causes, some acting directly on the kidney and others on its blood-vessels.

Cold is still regarded by many as of great, if not of paramount, importance in the production of this disease, and it has been supposed that cold resulting from exposure of the skin leads to extreme congestion of the deep-seated kidneys. Others have attributed the supposed influence of cold in the production of renal disease to the suppression of the functions of the skin, and to the retention in the blood stream of the toxic constituents of the sweat which should normally be excreted. The great variations in the quantity of urine excreted in the summer and winter have also been used as an argument in support of the opinion that there is some intimate connexion between the skin and the kidneys. At the present time there is no physiological evidence in favour of any reflex nervous connexion between the skin and the kidneys. That nephritis occurs after exposure to cold is undoubtedly, and, further, the disease may be unduly frequent in those whose occupations expose them to vicissitudes of temperature, as, for example, engineers and boiler-cleaners. Pneumonia is also a disease which may follow exposure to cold, but cold is no longer regarded as a direct and sole cause of pneumonia but simply as a disposing or assisting cause. In the case of pneumonia the cold is supposed to act by depressing the resistance of the organism as a whole, and thus allowing the pneumococcus to effect a lodgment. In many cases in which nephritis is attributed to cold, careful inquiry will often reveal the occurrence of some infective disease often of slight severity immediately antecedent to the supposed exposure to cold. Exposure to cold was once regarded as a cause of nephritis during convalescence from scarlet fever, but post-scarlatinal nephritis often occurs when the most careful precautions have been taken throughout, and the disease is not unknown in patients who have not been out of bed. It would seem probable that the part played by cold in the production of nephritis is hardly as important as has sometimes been thought, and that even when it is a factor in the production of the disease it may act rather as a disposing than as a direct exciting cause. On the other hand, there is abundant evidence that nephritis of all degrees of severity and of many different varieties can be produced by the action of toxic agents on the renal structures. When nephritis appears to follow directly upon exposure to cold it is probable that there is some toxic agency as well. This does not minimise the importance of cold as a factor in the production of the disease any more than in the case of pneumonia, but it relegates cold to the position of a disposing or auxiliary factor, and shews that it is not the sole or exciting cause. The same change of opinion has taken place with reference to the part taken by cold in the production of other diseases, as, for instance, pleurisy, pericarditis, peritonitis; these were all formerly attributed to the direct action of cold, particularly, perhaps, in the case of pleurisy. It is now realised that so-called idiopathic pleurisy is in the vast majority of cases due to the action of the tubercle bacillus, an infective agent; and it would seem probable that in nephritis a toxic

agent of some kind is also responsible for the production of the malady in a large proportion of the cases in which at first sight it would seem to be directly due to the action of cold.

The *toxic agents* capable of causing nephritis are very numerous and include various inorganic salts, especially compounds of lead and mercury and the bichromates; acids such as oxalic; organic substances such as alcohol, turpentine, and cantharides; and a number of animal and vegetable toxic bodies including snake venom, abrin, ricin, the blood of certain fish (more particularly that of the eel), and a body of considerable interest, vinylamine. A number of these substances are mainly of theoretical interest, inasmuch as though capable of producing nephritis experimentally, they do not cause the disease in the human subject. The toxins produced by various organisms belong to a more important category, and much experimental work has been done with the toxin of diphtheria. Nephritis follows a very large number of acute infections, and it is probable that in many instances it is produced by the action of a bacterial toxin. In some bacterial diseases it would seem probable that the active agent is the micro-organism itself, as nephritis may occur in a number of conditions, for example in tuberculosis, in which the organism causing the disease is found in the kidney and in the urine, although the toxin has but little action directly in causing nephritis. The number of toxic agents capable of causing nephritis is not only very great, but different toxins produce different varieties of lesions. According to Lindemann, three groups of renal poisons may be recognised—(i.) cantharides and the unknown virus of scarlet fever produce extreme glomerulo-nephritis; (ii.) the renal poisons containing the metallic salts and the oxides of the heavy metals lead to necrosis of the cells of the convoluted tubules; and (iii.) the renal poisons mainly of animal and vegetable origin, such as abrin and ricin and the blood of certain fish, produce degeneration and extensive vacuolation of the protoplasm of the epithelial cells of the kidney. Vinylamine produces results very similar to those seen after the administration of the bacterial toxins, and Lindemann states that the renal lesions produced by it are very similar to those seen after the administration of cadaverine and putrescine. This observation serves to explain the production of renal disease as a secondary result of the formation of toxic substances in the alimentary canal. In addition to these toxic agents capable of producing renal lesions, there is a further group of cellular toxins that have a similar action. The blood serum of an animal of one species when injected into another gives rise to very definite renal lesions; in other words, it is said to possess a nephrolytic action. This nephrolytic action can be greatly influenced by the injection into the animal of kidney substance prior to the withdrawal of its serum. Thus, the normal serum of guinea-pigs produces but slight effect on the kidney of the rabbit when injected into the latter animal, but the serum of the guinea-pig acquires nephrolytic properties if the guinea-pig be injected for some time with an emulsion of rabbit's kidney. In these circumstances the blood of the guinea-pig develops a nephrolysin.

These observations are mainly of importance as shewing the multiplicity and complexity of the toxic agents that may produce definite renal lesions akin to those seen in nephritis. But it has not been proved that the renal cells of an animal can lead to the production of a nephrolysin when they are injected into an animal of the same species as that from which they are derived. The blood of a guinea-pig will develop a nephrolysin acting on the cells of a rabbit's kidney when the latter is injected into the former, but the absorption by an animal of its own renal cells is a very different matter, and we do not know that in these circumstances similar toxic bodies are produced. Some experiments have been done to clear up this point, and it is stated that if the renal artery be ligatured on one side so that necrosis of one kidney results, lesions of a degenerative nature occur in the opposite kidney. Similar results are said to follow the ligation of one ureter, but here the conditions are more complex in that there is retention of urinary products on one side owing to the formation of a hydro- or pyo-nephrosis. It is, at any rate, determined that the lesions under these latter conditions of ligation of the renal artery or of the ureter on one side are very slight, and not comparable to those produced by the action of a nephrolytic serum prepared in the usual way by the injection of an emulsion of kidney. The experimental study of nephritis by the action of toxins not only shews that different lesions may be produced by different toxins, but it also has thrown some light on the relation of chronic renal lesions to acute. Such poisons as diphtheria toxin, corrosive sublimate, cantharidin, the toxin of *Staphylococcus pyogenes aureus*, may all produce acute lesions of varying degrees of severity, but provided the doses used be not excessive the kidney may regain its integrity after the subsidence of the acute phenomena. Notwithstanding these results Lyon was able to produce chronic lesions by the administration of small repeated doses, and thus it is probable that chronic disease is dependent upon the continuous action of some toxin rather than as a direct sequel of an acute lesion. Further, bichromate of potassium, which produces well-marked effects on the renal epithelium leading sometimes to its complete destruction, does not lead to the formation of any fibrous tissue in the kidney such as is seen in all forms of chronic nephritis. Since the injection of bichromate of potassium into the renal artery on one side may lead to the complete destruction of the epithelium of the tubules of that kidney without any fibrosis, the fibrous overgrowth seen in chronic renal disease can hardly be regarded as entirely dependent on the mere destruction of the tubular epithelium.

The toxic agents causing nephritis in the human subject may be taken in the form of food, drugs, or poison ; or they may be produced in the body, possibly as the result of disturbed metabolism ; or, finally, they may arise as the products of infective processes. With the exception of the possible action of cold, most agents giving rise to nephritis may be classified into one or other of these three groups. Alcohol is usually instanced as an article of diet capable of causing nephritis ; but there are the same difficulties in the way of explaining the effect of alcohol in the

production of nephritis as there are in the etiology of many other diseases imputed to this agent. Nephritis is undoubtedly a frequent occurrence amongst the intemperate, and instances have been recorded in which diffuse parenchymatous nephritis has followed rapidly after a short period of excessive drinking. On the other hand, large quantities of alcohol may be taken for long periods of time without the development of renal disease, either in an acute or in a chronic form. The malady, however, is frequently seen in those whose avocations expose them to temptation—for example, potmen and workmen who are exposed to great changes of temperature, and in whom both alcohol and cold may be factors in the production of the disease. Some forms of chronic renal disease, especially granular kidney, have been attributed to long-continued over-indulgence in food and drink, and this disease is said to occur as the result of high living. Some have attributed the chronic degeneration to the excessive quantities of animal food, but the etiology of granular kidney, or at any rate of some of its forms, is closely associated with that of arteriosclerosis and high tension. The long-continued ingestion of the heavy metals, either as medicine or sometimes in the form of poison, as in the well-known instance of lead poisoning, is unquestionably apt to produce nephritis or, at any rate, chronic renal disease. Mercury, lead, and arsenic are especially efficient in causing renal lesions. Turpentine and cantharides may cause nephritis, either when taken accidentally or intentionally as poisons, or even in some instances as the result of their medicinal use. Workers in aniline factories may be attacked by nephritis, as the result of inhalation of, or the swallowing of, the benzene derivatives. Cantharides is said to have produced nephritis in several instances in which the drug has been employed simply as a vesicant; and nephritis has followed the use of turpentine in the treatment of intestinal haemorrhage or of purpura.

Nephritis is not uncommon in the course of certain chronic diseases involving disturbance of metabolism, more especially gout and diabetes. The etiology here is by no means obvious, but it is usually supposed to be due to the irritant action of some toxic agent in the blood. The relation of nephritis to gout is obscure, inasmuch as it is so inconstant, and very severe gout may exist for long periods of time without the development of nephritis. On the other hand, chronic parenchymatous nephritis and granular kidney in one or other of its forms may be present in the gouty. Nephritis is not an uncommon complication in diabetes, and usually takes the form of chronic parenchymatous or diffuse nephritis; but acute nephritis of a very severe grade, with sudden onset and haematuria, sometimes occurs, and a chronic lesion, such as granular kidney, may also be found associated with diabetes. Nephritis is not uncommonly associated with hepatic diseases, but here the explanation may be that both the affections are due to the same agent—for example, alcohol. A certain degree of albuminuria and the passage of casts is often seen in jaundice, and the phenomena are regarded as due to the irritation of the kidney by the bile; a high degree of nephritis, however, is not generally produced.

Lead is the heavy metal that most frequently gives rise to renal disease, now that the action of mercury is more thoroughly understood, and its use in medicine and the arts more carefully restricted. Lead can be shewn experimentally to produce necrosis of the renal epithelium of a widespread character. Lead causes especially chronic renal disease, and the lesion is a mixed one, partly tubal, partly interstitial. One of the varieties of the contracted white kidney is not infrequently dependent on the action of this poison. The disease is generally seen in those who have been exposed to the long-continued absorption of small quantities of lead, as in painters, fitters, and even such an occupation as the making of artificial flowers.

Nephritis occurs as a complication of *pregnancy*, usually in the later months. The etiology of this form of nephritis is obscure, and at one time it was attributed to purely mechanical causes, such as the pressure of the enlarged uterus on the renal veins. An argument in support of this was afforded by the rapid disappearance of the albuminuria and other phenomena after the emptying of the uterus; but it is difficult to understand how a mere mechanical condition can produce not only albuminuria but all the severe effects associated with nephritis, especially as in many instances there is no evidence of any undue distension of the abdomen or compression of its contents. The view is very generally held now that the nephritis of pregnancy is really of toxic origin, although the nature of the toxin is quite unknown. The nephritis of pregnancy is remarkable in many respects, and especially perhaps in the rapid manner in which it frequently subsides after delivery, even in cases with extensive dropsy and marked retinal changes.

The most important agents in the production of nephritis, however, are those included in the third group, in which the disease arises as a *sequel to an acute infection*. Nephritis may arise as a complication of almost any acute infective process, but it is especially correlated with the acute specific fevers, and most of all with scarlet fever. This relationship is seen especially in nephritis affecting children. Although scarlet fever stands out conspicuously as an acute specific fever in which nephritis is most likely to occur, yet this complication is also seen after other acute specifics, for example, measles, mumps, enteric fever, rheumatism, erysipelas, diphtheria, and chicken-pox. In most instances nephritis occurs somewhat late in the course of the acute specific infection, and sometimes even when convalescence is approaching. On the other hand it may appear early in the course of the disease. One of the most remarkable points is that the occurrence of nephritis is not determined apparently by the severity of the acute infective process. Some of the most severe cases of nephritis may occur as complications of a mild attack of scarlet fever. In a very large proportion of cases of nephritis careful investigation will reveal the occurrence of an acute infection immediately before the onset of the symptoms of the renal disease. In a large number of cases the infection is so slight as scarcely to have attracted attention at the time, and this is especially liable to be the case where

the malady is such a one as tonsillitis, influenza, or merely a catarrh, such as a severe cold in the head. *Syphilis* is another infection in the course of which nephritis may occur, and in which, for a variety of reasons, the syphilitic nature of the case may be entirely overlooked, and the disease attributed to cold. Nephritis arises during the secondary stage of syphilis, and generally within the first year, or at the most two years, from the infection (*vide* p. 693). It has been thought that granular kidney in early youth is usually a parasyphilitic lesion of inherited syphilis (Payne). Nephritis may arise in the course of other acute infections, as, for example, pneumonia, but it is especially associated with the acute exanthems.

Nephritis of a severe type usually arises during the later stages of the acute infective processes at a time when convalescence from the acute disease is approaching. In scarlet fever nephritis occurs most frequently during the second week; the febrile albuminuria dependent on transitory nephritis, a much milder affection, occurs in the earlier stages of the acute infective processes during the height of the fever (*vide* Vol. II. Part I. p. 456). Exposure is often thought to be a factor in the production of severe nephritis during convalescence from scarlet fever, and in many instances in which the scarlet fever is not severe, the renal complication has been regarded as dependent on the patient getting up and about too soon. Nephritis, however, undoubtedly occurs in cases in which the greatest care to avoid exposure and chill has been taken. There can be no doubt that the renal lesion is dependent on the action of a toxin. Severe nephritis sometimes occurs as a complication of diphtheria, and then presents all the usual features, such as albuminuria, dropsy, and uraemia. This is on the whole a rare complication of diphtheria, and occurs late in the course of the disease, and must be distinguished from the intense albuminuria that is an almost invariable accompaniment of diphtheria, and occurs as early as from the third to the fifth day in the disease. This albuminuria of diphtheria is remarkable in that the amount of albumin in the urine is generally large, and greater than that seen during the height of other acute febrile diseases. Notwithstanding this the albuminuria rapidly clears up, and is not followed by any of the other signs or symptoms of renal disease. This albuminuria is clearly of toxic origin, and does not lay the foundation of future renal disease. A much more severe affection is sometimes present; in such instances the urine diminishes in quantity, and complete suppression may ensue, and the patient frequently rapidly succumbs to the toxæmia. There is yet another class of case: a nephritis resembling in its severity that due to scarlet fever and other causes may develop in the case of diphtheria, and lead to progressive or permanent renal lesions.

I. ACUTE NEPHRITIS

SYNOMYMS.—*Acute, desquamative, parenchymatous, tubal, or diffuse Nephritis.*

The gross **morbid anatomy** of acute nephritis depends in great measure on the duration of the disease. In the early stages the vascular phenomena are extremely well marked, but in the later stages of the affection the degenerative changes in the epithelium become much more obvious. But even in the earlier stages the extent of the vascular changes varies within wide limits. It would also seem as if the post-mortem appearances differ to some extent according to the etiology of the malady. Thus, the appearances presented by the kidneys in acute scarlatinal nephritis differ materially from those seen in the acute nephritis sometimes complicating enteric fever, diphtheria, and other infective diseases. Great as the differences are, they usually depend mainly on the degree of vascular engorgement and of degenerative tubal changes respectively.

In acute nephritis terminating fatally within a week or two of its onset the kidneys are considerably enlarged and extremely congested, the increased vascularity being specially prominent in the pyramids and in the stellate vessels of the capsule; the swelling of the organ is such as to cause great stretching of the capsule, so that on incision the renal substance gapes. The kidneys may be swollen so as to have doubled their normal size, and they may weigh as much as one pound each. In addition to extreme congestion there may be haemorrhages, both beneath the capsule and into the substance of the organ; and sometimes these haemorrhages are so numerous as to be scattered all over the surface, throughout the substance of the kidney, and to occur in the renal pelvis. These haemorrhages are usually small, approximately the size of a pin's head. The congestion is usually sufficiently marked to make the glomeruli visible to the naked eye as bright red spots. The capsule strips off readily, leaving usually either an extremely congested or a marbled surface. On section the surface of the kidney substance, especially of the cortex, may be somewhat granular, and the distinction between the cortex and the medulla is usually well marked, but the cortex is obviously swollen and increased in width, and often opaque in appearance.

On microscopic examination changes are found in the glomeruli, the tubules, and the interstitial tissues. All the vessels of the kidney are dilated, and numerous extravasations of blood-corpuscles may be seen in the interstitial tissue, and in the interior of the tubules and of the glomeruli. The interstitial tissue is also oedematous, the tubules being separated from one another to a greater extent than normally. The glomerular vessels shew hyaline degeneration, and the glomerular chamber is frequently filled with a mass of blood-corpuscles and desquamated epithelial cells. An inflammatory exudation may also be present in the

loops of the glomerular tuft, and the epithelium lining the glomerular chamber has undergone proliferation, so that very commonly a mass of cells intervenes between the lining membrane of the capsule and the vessels of the tuft. This mass is very liable to appear crescentic in sections, and is one of the more characteristic appearances of acute nephritis. The vessels in the capillary tuft are not uncommonly thrombosed. The connective tissue separating the tubules also shews evidence of the inflammatory process in the form of congestion and exudation, and these changes may be especially well marked round the glomeruli. The glomerular changes are not equally prominent throughout the kidney; here and there areas may be seen where the intensity of the morbid process is greater, and others where it is less; in fact this want of uniformity in the distribution of the lesions is extremely characteristic of nephritis. The changes in the tubules are specially notable in the cortex, although they are not necessarily limited to this region. The tubules are dilated, and the epithelium not only presents necrotic changes, but in many instances is shed. In some forms of acute nephritis the epithelium is lost in such a large number of tubules as to give rise to the name desquamative nephritis. The shed and disintegrated epithelium is liable to accumulate in masses in the interior of the tubules and to block them up. This is one of the causes of the dilatation of the tubules and of the increase in the size of the kidney observed in this disease. The epithelial cells shew a number of changes; thus, in some regions cloudy swelling and fatty change may be pronounced; in others the cells have lost their characteristic elaborate structure with the well-known striated border, and have become hyaline or glass-like in appearance. Very commonly the epithelium of the cortex presents simple necrotic changes. The tubular changes like those in the glomeruli vary in the degree of their development in different parts of the kidney; the cavity of the tubules is filled with the detritus formed by the desquamation and disintegration of the renal cells, with blood-corpuscles, and coagulated protein. The lesions in the medulla are essentially of the same character, though not usually developed to the same degree; in this region the changes in the interstitial tissue are especially well observed. There are great individual variations in different instances and in different forms of acute nephritis in the degree of interstitial change present. In some instances the inflammatory exudation in the interstitial tissue is extremely well marked and multiple haemorrhages are present. In rare instances, to which the term lymphomatous nephritis has been applied, there are large collections of leucocytes in the interstitial tissue. This form of nephritis is especially seen as a sequel of enteric fever.

The inflammatory changes in the interstitial tissue are especially marked in the vicinity of the blood-vessels; in acute nephritis of two or three weeks' duration distinct evidence of periarteritis may be observed, and in the course of a month to six weeks from the onset of the disease endarteritis may be very obvious. The changes in the arteries are not limited to the renal vessels although most marked in

these, but it is more especially in chronic Bright's disease that the lesions in the vessels of the body generally are so distinct. Some cases of acute Bright's disease pass gradually into chronic Bright's disease, and death occurs within some six weeks or three months from the onset of the symptoms. It is in such cases as these that the lesions in the vessels are especially obvious, although perhaps it is difficult to say whether they should be described as associated with acute or with chronic nephritis, as it is difficult, if not impossible, to draw a sharp line between these two conditions.

Symptoms.—One of the difficulties in distinguishing between acute and chronic nephritis is that the onset of acute nephritis is not always marked by very urgent symptoms, and the term is sometimes applied to all cases in which such symptoms as are present have developed suddenly. There can be little doubt that in many of these cases the disease is really chronic and has been present for a considerable time. Nephritis is sometimes ushered in with severe symptoms, more especially when it complicates some acute infection. A general malaise or feeling of intense illness with aching in the loins are common initial symptoms. Pyrexia is not a marked feature, and very often there is no rise of temperature, and it is very exceptional for the malady to be ushered in with a rigor. Vomiting may be present and is sometimes severe, but the symptoms on the whole are vague and indefinite and in a very large proportion of cases even of acute nephritis the first intimation of the presence of the disease is afforded rather by the presence of physical signs than of symptoms. Thus, in one set of cases the first indication of the presence of even severe acute nephritis may be the passage of smoky and blood-stained urine, in others the occurrence of dropsy especially of the face with or without haematuria. In not a few instances albuminuria is the sole evidence of the occurrence of nephritis, neither dropsy nor haematuria being present, and the symptoms being so slight as to escape observation. Thus, the onset of acute nephritis is often overlooked, and it is only after the lapse of some days that with the progressive development of further symptoms the condition is recognised.

Several varieties of acute nephritis may be recognised according to the severity of the symptoms present, and acute nephritis may probably be divided into two groups according to the presence or absence of anasarca. Neither the extent of dropsy present nor even its presence can be correlated merely with the severity of the nephritis. Some of the most intense forms of acute nephritis may run their whole course without any dropsy, and on the other hand very extensive dropsy may be seen in patients in whom neither the constitutional condition nor the changes in the urine would point conclusively to the presence of a very severe lesion. Acute scarlatinal nephritis may lead to a most extensive destruction of the kidney elements and excretion of a very scanty, albuminous, and highly blood-stained urine, and the development of severe uraemia, and yet there may be no dropsy. In other cases dropsy is the leading feature of the illness, and there is no change in

the urine beyond a diminution in its quantity and the passage of a moderate amount of albumin and casts. The relation of these two forms of nephritis, one with and the other without dropsy, to one another is obscure; it is often thought that the differences observed are merely dependent on the differences in the severity of the lesion, but this can scarcely be so, since as already stated very severe and even fatal nephritis may occur without anasarca. Further, anasarca is sometimes the first sign of illness, and although doubtless in some instances an earlier change in the urine may have been overlooked, yet this can scarcely be always the case. It must be admitted, however, that if there are these two forms of nephritis, one with and the other without dropsy, no marked difference in the etiology is present, since both forms may occur as complications of the same illness or as the result of the action of the same poison.

In acute nephritis the quantity of *urine* is almost invariably greatly diminished, and not uncommonly there is suppression which may be rapidly fatal. Acute nephritis of a very severe grade may occur, however, as a complication of diabetes without the quantity of urine undergoing any great diminution, and this although the urine is loaded with albumin and blood. The diminution in the quantity of urine is thus not necessarily accompanied by the development of dropsy, but the onset of dropsy is necessarily accompanied by a diminution in the urinary flow. This is the reason why so many observers have regarded the dropsy as the direct result of the diminished flow of urine. The extent of the diminution in the quantity of urine varies within wide limits. In very severe cases a few ounces only of blood-stained highly albuminous urine are passed in the twenty-four hours, and in not a few this condition goes on gradually to complete suppression. In the majority of cases of acute nephritis of moderate severity the quantity of urine is diminished approximately to one-half the normal.

In addition to the general symptoms of illness, the occurrence of dropsy, and the excretion of an abnormal urine, most cases of acute nephritis shew some symptoms of *uraemia*. In a slight case the most common uraemic phenomena are headache and vomiting, which is especially apt to be severe, serious, and refractory to treatment. In nephritis of a high degree of severity very much more formidable uraemic symptoms such as dyspnoea, twitchings, epileptiform seizures, maniacal excitement, drowsiness, and coma may develop and not uncommonly prove fatal, although acute uraemia in the course of acute nephritis is not so severe and dangerous a phenomenon as when it complicates chronic renal disease. The onset of uraemic manifestations in acute nephritis is usually gradual and preceded by a period in which vomiting is the most prominent symptom. Twitchings of the muscles of the hand and arm, slight drowsiness, and some dyspnoea of a hissing type then supervene. Very severe epileptiform seizures not uncommonly supervene extremely suddenly, but they may be repeated and the seizures go on at intervals for some twenty-four to thirty-six hours.

Although in many instances these epileptiform seizures begin locally they soon become generalised. The epileptiform seizures of *uraemia* are closely similar in character to the fits seen in *eclampsia*, and in fact the latter condition is now regarded as *uraemic*. These epileptiform seizures are especially characteristic of the *uraemia* of acute *nephritis*, and although they are often very severe and give rise to great alarm, recovery is not uncommon. *Amaurosis* or complete blindness without any changes in the fundus is also common in acute *uraemia*, and is supposed to be toxic inasmuch as complete recovery of vision often takes place. The onset of the *amaurosis* is sometimes very sudden ; it is accompanied by marked dilatation of the pupil and may be the initial symptom of the onset of acute *uraemia*. Although drowsiness passing into *coma* is on the whole the most common *uraemic* manifestation, a very remarkable form of restlessness together with complete sleeplessness is sometimes seen in cases of *uraemia* associated with acute renal disease. In such patients the other *uraemic* manifestations include such symptoms as dyspnoea, twitchings, and a subnormal temperature, and death may occur in such cases without any preceding unconsciousness.

Dropsy in acute *nephritis* varies much in its severity, and, as already mentioned, it may be absent notwithstanding the presence of very extensive *nephritis*. The dropsy of renal disease is characterised by being especially marked in the subcutaneous tissue, and in some instances a very high degree of *anasarca* may be present without there being any large quantity of fluid in the serous cavities, but it is probable that there is always some increase in the quantity of fluid in the peritoneum, and in the pleurae in cases with any considerable *anasarca*. It is not possible by clinical methods to determine with certainty the presence of small quantities of fluids in the serous cavities, and hence it often seems as if the dropsy were entirely subcutaneous. There is, however, a great difference between cases of cardiac and renal dropsy ; in cardiac disease a high degree of *anasarca* of the trunk does not exist without a correspondingly large amount of dropsical effusion in the serous cavities ; in renal disease this is not the case, the face, the arms, and the trunk, as well as the legs, may be swollen to a great extent, so much so that the patient may be unrecognisable, and yet the pleura and the peritoneum may contain moderate quantities only of fluid. The *anasarca* of renal disease is most marked where the areolar tissue is most loose, and hence *anasarca* of the scrotum and of the face is especially characteristic of the disease. In patients confined to bed great swelling of the loins and of the lower part of the back, especially over the sacrum, may take place, and dropsy in this position may be overlooked unless a general examination be made. Patients suffering from acute *nephritis* often first notice a swelling in the face on getting up in the morning, but in other instances the swelling is noticed first in some other part of the body, and even in the legs. The degree of swelling may be such as to cause cracking of the skin, but this is very unusual. More generally the

dropsy is quite painless, notwithstanding the great swelling of the part. The onset of the dropsy is always accompanied by diminution in the quantity of urine, and very often the approaching convalescence of the patient and the subsidence of the dropsy are first detected by noticing an increased urinary flow. It is difficult to estimate variations in a dropsy by merely observing the patient and noticing the degree of swelling or of pitting on pressure. The most accurate method available is that of weighing the patient, an increase in weight indicating an increase in dropsy. Not uncommonly such patients may increase in weight several pounds in the course of a few days. As already mentioned, where the anasarca is large in amount fluid is also found in the serous cavities, and in some instances of acute disease ascites and hydrothorax may reach a high degree. Large dropsical accumulations in the serous cavities are, however, more characteristic of certain forms of chronic nephritis than of the acute malady. In exceptional instances the serous effusions are very large in amount when the general anasarca is but scanty, and in some cases ascites is a very prominent feature of the illness without the presence of any excessive amount of general anasarca. This condition, however, is also more often seen in chronic renal disease than in the acute variety. In severe cases of acute nephritis accompanied by much general anasarca, and running a fatal course, large quantities of fluid may be found after death in all the serous cavities. The dropsy of renal disease is, however, not confined to the subcutaneous tissue and the serous cavities ; it may also affect the solid organs and more especially the lungs and the brain. Pulmonary oedema is a common accompaniment of serious acute nephritis, and it is especially apt to be marked in uraemic cases ; in fact the hissing respiration of uraemia has been attributed by some to pulmonary oedema. Pulmonary oedema is especially prominent in cases in which general anasarca and effusion into the serous cavities are well marked, but it may be present to a very considerable degree when these phenomena are not excessive in their development, and it is practically an invariable accompaniment of fatal uraemia. Oedema of the brain is also often present, and a very large excess of fluid is found bathing the cerebral convolutions at the autopsy. The ventricles of the brain are also frequently distended. Oedema of the glottis has also been described as a not uncommon complication both in acute and chronic renal disease, and no doubt this complication sometimes occurs, but in some instances the dyspnoea attributed to oedema of the glottis may have been really of toxic origin, and it must be remembered that inflammatory complications of the glottis are not uncommon in renal affections (*vide Vol. IV. Part II. p. 192*). The dropsical fluid of renal disease is poor in protein matter and rich in salts and extractives. The composition of the fluid varies according to the part of the body from which it is derived, that from the subcutaneous tissue containing less protein than that from the serous cavities ; in this respect renal dropsy resembles other forms, e.g. cardiac, but the dropsical fluid of renal disease is always less rich in protein and

richer in salines and extractives than the fluid obtained in cardiac cases from similar parts of the body (*vide p. 520*).

Although *cardiovascular* complications are most characteristic of chronic renal disease, yet even in the acute affection some cardiovascular changes are produced. A certain degree of high blood-pressure and of cardiac hypertrophy may appear within a few weeks of the onset of acute nephritis, and characteristic signs of cardiac hypertrophy may be detected within six weeks of the onset of the renal disease. A hardness of the pulse and a notable degree of increased pressure may be found within a few days of the onset of acute nephritis, and this perhaps is especially well seen in cases complicating scarlet fever. Cardiac hypertrophy, however, is not the only lesion that may develop in the course of acute renal disease; in not a few cases myocardial degenerative changes take place, and cardiac dilatation of a greater or less degree of severity ensues, and in some instances is of sufficient severity to cause death. Cardiac dilatation from myocardial degeneration occurs not only in acute but also in chronic renal disease. In these latter circumstances it is a complication or sequel of cardiac hypertrophy, and thus is apt to be well marked, and to produce serious symptoms in cases with notable cardiac hypertrophy. This form of cardiac dilatation is especially frequent in the later stages of granular kidney, and causes the clinical picture of this disease to resemble in many instances that of cardiac disease.

Although high blood-pressure is very commonly associated with the cardiovascular changes present in renal disease, yet a notable increase in the arterial pressure may be present, especially in acute renal disease, at a time when there are no physical signs of gross changes in the heart and arteries, and this has led many authorities to regard the arterial changes as secondary effects resulting from the increased blood-pressure; this increased pressure is supposed to be dependent upon a heightened activity of the vasomotor system, possibly brought about by the action of some toxic substance. In the later stages of chronic renal disease very extensive lesions of the arteries may exist, resulting in great thickening of their walls, and yet the blood-pressure may not be materially raised. Symptoms dependent on these cardiovascular lesions are more often present in chronic than in acute renal disease. One of the most constant is the well-known headache associated with high blood-pressure; it is usually diffuse and often very severe and constant, and greatly aggravated by any change of posture, and hence liable to be marked on rising in the morning. Headache in chronic renal disease is very apt to be attributed to uraemia, and, doubtless, often is associated with such poisoning. In a large number of cases, however, it is dependent on purely vascular causes, as is shewn by the relief obtained by any measure causing a fall of blood-pressure, such as smart haemorrhage from the nose, free action of the bowels, or the administration of nitrates and other drugs leading to a fall in blood-pressure. Patients suffering from high blood-pressure and the associated arterial degeneration are liable to

haemorrhage in various situations, especially, perhaps, the nose and the retina, occasionally from other mucous surfaces, and in some instances even from the mucous membrane of the pelvis of the kidney, the so-called renal epistaxis of Gull. In some instances haemorrhage of a slow and continuous character takes place in the mucous membrane of the mouth and gums ; this, however, is more associated with local conditions of the mouth, stomatitis, than with increased arterial pressure.

Disturbances of sight are common in all forms of renal disease, acute and chronic, and in some exceptional instances visual disturbance is the first symptom that attracts the patient's attention. Impairment of sight, however, may arise from other causes, for example uraemic amaurosis, which may occur in acute and chronic renal disease. Other uraemic symptoms are usually present in these cases, but sometimes the amaurosis is the initial manifestation of the uraemic state. This uraemic amaurosis is, perhaps, especially seen in the nephritis of pregnancy. It would seem that in some cases of blindness associated with the nephritis of pregnancy a retro-bulbar neuritis was present, inasmuch as the condition does not clear up, and may be followed by the appearance of optic atrophy. Little is known as to the occurrence of albuminuric retinitis in association with true acute nephritis, that is to say, acute nephritis affecting previously healthy kidneys. There is, however, one exception to this, namely the nephritis of pregnancy. Not only does albuminuric retinitis occur comparatively frequently in the nephritis of pregnancy, but it would seem that the prognosis as to the duration of life in these cases is better than in cases in which albuminuric retinitis complicates ordinary chronic nephritis. Thus, Mr. Nettleship mentions 22 cases of albuminuric retinitis in pregnancy, and in only one instance did death occur within two years of the recognition of the disease, and two-fifths of the cases were known to have lived for two years or more after the onset of the retinitis. On the other hand, in 42 cases of retinitis not associated with pregnancy one-fifth only of the cases lived for more than two years, and no less than 25 died within the year from the time of the recognition of the ocular changes.

The diagnosis of acute nephritis does not usually present many difficulties, but occasionally the condition may be confounded with infarction and passive congestion, especially in cardiac disease, and in some cases it may be difficult to distinguish between acute nephritis and chronic nephritis which has run a latent course, and then suddenly has led to the development of acute symptoms. Further, it may be difficult to distinguish cases of transitory nephritis, or so-called febrile albuminuria, arising in the course of acute infections. These cases are, however, to all intents and purposes cases of nephritis, and they only differ in degree from the more serious forms of acute nephritis arising in the course of the same illnesses.

When dropsy and a scanty, smoky, and highly albuminous urine are present, the diagnosis is easy, and such difficulties as present themselves are in cases in which either dropsy is absent, or the urine does not

present the characteristic smoky tint. In transitory nephritis the urine is simply albuminous, dropsy being absent, and haematuria usually absent, or, if present, only to a very slight extent. In some instances of acute nephritis, however, the urine is highly albuminous, and may contain a large quantity of blood, and dropsy may be completely absent. Such cases present considerable resemblance to infarction of the kidney, and the diagnosis must then generally rest on the course of the case; in infarction the urinary changes occur with great suddenness, and frequently disappear equally suddenly without the manifestation of any general symptoms of severe illness. Not uncommonly in infarction the urinary changes last a few days only, although it must be admitted that a slight albuminuria may persist for a considerable time. Much assistance is afforded by the occurrence of pain in the renal region, and also by the coexistence of some cause such as heart disease capable of leading to infarction. In passive congestion of the kidneys in heart disease considerable haematuria may occur from time to time with the presence of numerous blood-casts and the excretion of a highly albuminous urine. Such patients may also present dropsy of the cardiac type, and it may be difficult to determine with certainty, at any rate for a time, whether acute nephritis is present, or mere passive engorgement. The course of the case and the existence of the cardiac lesion will often afford much assistance in the differential diagnosis. Further, the urine in passive congestion will not usually present the great variety of casts of epithelial origin that are associated with acute nephritis. The confusion of infarction and passive congestion with acute nephritis is usually dependent on too much stress being laid by the observer on the presence of blood in the urine. It is much more difficult to distinguish between cases of acute nephritis and certain cases of chronic nephritis with sudden manifestation of symptoms. Thus, dropsy may occur with great suddenness and severity in cases of chronic tubal nephritis, and the patient's history may therefore suggest that the disease is acute. The changes in the urine may be very similar, in both acute and chronic nephritis, the quantity may be greatly diminished, and much albumin may be present and blood absent. In most cases the differential diagnosis has to be made on the presence or absence of cardiovascular changes. High blood-pressure may be present within a short time of the onset of acute nephritis, but appreciable enlargement of the heart, or the presence of distinct thickening of the vessels, or the existence of marked changes in the fundus oculi, will all point to the conclusion that a chronic lesion of some standing is really present.

In some very exceptional cases, more especially in children, a generalised oedema similar to that seen in acute nephritis may come on, and yet examination of the urine fails to reveal the presence of any albumin. In some of those cases which have proved fatal renal lesions similar to those of acute nephritis have been described. Such cases must obviously present great difficulties in diagnosis.

It is sometimes possible to recognise cases of syphilitic nephritis

on account of the presence of some associated syphilitic lesion, or because the patient has recently suffered from primary syphilis, or, lastly, from the peculiar character of the illness. Thus, many cases of syphilitic nephritis present an extraordinarily intense albuminuria with few other signs ; dropsy may be absent, even marked disturbance of the general nutrition may also be absent, but the urine is loaded with albumin, not uncommonly becoming solid on boiling. This condition may persist for weeks, sometimes even for months, without the development of any other marked signs of illness. In such cases the possibility of the presence of syphilitic nephritis should be entertained inasmuch as these cases not uncommonly react to specific treatment in a remarkable manner, even when the albuminuria has been intense and has lasted for many months.

The prognosis is somewhat uncertain, but, speaking generally, it is favourable as to life ; it depends to a considerable extent not only on the severity of the affection, but also on the cause of the nephritis. Thus, the acute nephritis of scarlet fever, and the true acute nephritis seen exceptionally in diphtheria, may be fatal, and in some instances very rapidly fatal. On the other hand, in a considerable proportion of cases the symptoms subside, and in the course of time even the albuminuria may disappear ; but such patients not uncommonly suffer from subsequent attacks which may not clear up with equal facility.

During the acute stage the prognosis depends very largely on the degree of suppression of the urinary excretion present, and the outlook is very serious where the patient passes but a few ounces of highly albuminous blood-stained urine. Further, the association of secondary inflammations, such as pericarditis, pneumonia, and pleurisy, is of grave omen. In some cases death occurs from cardiac dilatation dependent on myocardial degeneration, and hence a rapid feeble pulse and a fluttering cardiac impulse are serious signs.

Recovery may take place in cases with very considerable dropsy, and also in cases with acute uraemia often of a severe character. Acute uraemia, even of the eclamptic type, is by no means so serious in acute nephritis as it is in the chronic disease.

It is often stated that if the albuminuria persists for as long as six months it will probably be permanent, but this is not really necessarily the case, and instances may occur in which an albuminuria lasting for far longer than this, even for periods of one and two years, may ultimately entirely disappear ; doubtless, however, such cases are not very usual.

Treatment.—The patient must necessarily rest, and care should be taken that he is kept sufficiently warm to promote the action of the skin. It is also advisable that he should be clothed in flannel garments to avoid any chill. The diet should be restricted to milk, gruel, and barley water, at any rate during the acute stage, as it is advisable to diminish the work of the kidney as far as possible, and in the case of adults there is no harm in restricting the diet to from one to two pints of milk in the twenty-

four hours. Such a restriction in diet cannot of course be maintained for any very prolonged period, but in most cases the appetite is poor and nausea is often present, so that there is no great desire to take food. Some authorities have advised withholding all food and only giving water for a period of one to three days, and good results have been said to have been obtained in this way by diminishing the work of the kidney to the utmost. All writers are agreed that meat extracts, meat soups, and beef-tea are of no advantage and possibly prejudicial in acute nephritis, inasmuch as their nutritive value is low and these preparations are liable to contain considerable quantities of nitrogenous extractives. The milk given should be diluted with water, soda water, or barley water, and especially in cases with nausea or vomiting it should be given in small quantities at a time. The milk may be thickened with farinaceous food, such as arrowroot, and when the patient dislikes milk probably no harm will be done by flavouring it with tea or coffee, although there may be theoretical objections to the use of either of these agents, inasmuch as they are diuretics. The patient should be allowed to drink freely of water and lemonade, or alkaline waters may be given to relieve thirst. All authors are agreed that alcohol should be prohibited. The usual treatment of the disease in this country is conducted on the above lines, but abroad, and especially in France, objection has been taken to a milk diet even in the treatment of acute nephritis owing to the considerable quantity of salts contained in milk, and the view is held that the dropsy so often present in acute nephritis may be aggravated by a free milk diet. A diet consisting largely of bread, vegetables, and eggs has been advised, as, provided the bread is specially prepared, such a diet contains but small quantities of chloride of sodium, and it is thought that somewhat better results are obtained with it. Such a diet, however, is unsuitable during the acute stage, or, at any rate, the most acute stage of the disease, but there can be little doubt that in cases of some standing no great benefit is obtained by keeping the patient for a prolonged period, as used to be the custom, on a milk diet exclusively. Very considerable quantities of milk are necessary in order to provide sufficient energy for the body, and it is conceivable that with these large quantities of fluid the tendency to hydraemic plethora may be increased. The main principles unquestionably are to diminish the diet as much as possible during the first few days of illness, and then to provide a diet with as little nitrogenous content as possible.

The activity of the skin should be promoted, but it is often difficult to produce sweating in renal disease even by the administration of powerful drugs. Hot packs and hot-air baths may be used for this purpose, especially in the cases in which the quantity of urine is greatly diminished and uraemia is present or imminent. If hot-air baths are used, care should be taken that at any rate at first the temperature should not be too high, inasmuch as faintness may be produced, and a temperature of 120° F. is sufficient at any rate for the first bath. Sudorifics may be employed, more especially jaborandi or small doses of pilocarpine. There

is some difference of opinion as to the value or advisability of using pilocarpine. The skin of many patients with Bright's disease does not readily sweat, and large doses of pilocarpine have to be employed in order to produce a marked effect. In these circumstances a considerable degree of bronchorrhœa may be induced, the pilocarpine causing marked secretion in the respiratory tract, and some embarrassment of the respiration may occur from this cause.

It is essential that the bowels should act freely, and the want of action of the kidneys can be compensated for more readily by increasing the excretion from the alimentary canal than by promoting the secretion of sweat. Some authorities object to the use of mercurial purges in renal disease, on the ground that mercury may damage the kidney and even cause nephritis. This objection, however, is rather theoretical, and there is really no evidence that the occasional administration of a mercurial purge is in any way prejudicial in either acute or chronic renal disease. In some forms of nephritis, especially syphilitic nephritis, mercury may be prescribed with great benefit in the ordinary way in which it is used in other specific lesions. At the commencement of acute nephritis much good may be done by the administration of a smart mercurial purge such as calomel. Subsequently the daily purgative action may be maintained by the administration of salines in the form of sulphate of magnesium, compound jalap powder, or sulphate of sodium. Salines are peculiarly useful, especially when given in a concentrated form, on account of the copious watery motions that result from their action. In most cases of acute nephritis no further treatment is required, and with the subsidence of the disease the diet may be gradually increased, and as convalescence approaches, tonics, especially iron and possibly arsenic, may be prescribed with benefit.

Complications, however, may occur which may demand further treatment, and this is more especially the case with reference to dropsy and uraemia; the dropsy may be treated by the measures described above, more especially free purgations, and it would seem that much benefit may be derived, at any rate in some cases, by taking care that a minimum of chloride of sodium is ingested. Where dropsy is well marked the case is usually one of some duration, and the acute symptoms have probably to some extent subsided although the dropsy persists. It is in these cases especially that a relatively dry farinaceous vegetable and more or less salt-free diet should be ordered. A cautious trial may also be made with diuretics, although perhaps on theoretical grounds there is much to be said against stimulating the kidney. Still, some drugs, such as digitalis, produce a marked diuretic effect not so much by direct action on the kidney as by improving the efficiency of the circulation; certainly in cases of persistent dropsy a trial should be made to see whether digitalis leads to an increase in the urinary flow, but it is no use persisting in the administration of the drug if no such effect is produced. Further, a trial may also be made with a more potent diuretic, such as citrate of caffeine. This, however, should be given cautiously,

and its use not persisted in unless a very distinct and direct effect is produced. The action of caffeine on the kidney is complex : in small and initial doses it produces a well-marked diuresis, but large doses or the continued administration even of small doses may lead to the opposite effect, namely, a scanty excretion, and some have supposed that the headache and vomiting occasionally seen after the prolonged administration of caffeine may depend on the retention of urinary products. The dropsey may be so extensive and generalised that it may be necessary to remove the fluid by surgical procedures. Large accumulations in the chest leading to embarrassment of the respiration should certainly be withdrawn by paracentesis, and it may be necessary in some instances of very extensive generalised anasarca to remove the fluid either by Southeys' tubes or by incisions. Such procedure is however but rarely required in acute nephritis, and from the great risk of secondary infections such methods of treatment should not be employed unless there is very urgent necessity.

Uraemia must also be treated by the general measures indicated above, such as hot-air baths and free purgation. If these measures are unsuccessful, and especially if epileptiform seizures are present, some sedative drug such as chloral should be administered, if necessary by the rectum. Chloroform may also be of much service, and in the eclamptic attacks associated with the nephritis of pregnancy morphine may be of great value. Many practitioners dread the use of morphine in the treatment of uraemia of ordinary renal disease. It is, however, certainly often of great service, more especially for epileptiform seizures ; the main contra-indication to the use of morphine is the existence of pulmonary complications, for morphine is singularly dangerous in all conditions in which the respiration is impaired. Uraemia in acute nephritis may be treated very successfully with venesection ; the results are far more successful than in the uraemia of chronic renal disease.

II. CHRONIC NEPHRITIS

(LARGE WHITE KIDNEY AND CONTRACTED WHITE KIDNEY)

General Considerations.—In chronic Bright's disease the kidneys present very great variations both in their naked-eye and microscopic appearances. Thus, the organs may be large, smooth, pale or mottled in colour, or, on the other hand, they may be small, granular on the surface, and of a brownish-red hue. The weight of the organ may vary from an extreme of one pound to as little as an ounce and a half or even an ounce. Although there are these wide differences between representative specimens of the two extremes, there is no difficulty in collecting a series presenting points of considerable general resemblance between the two extremes. These discrepancies account for the considerable difference of opinion that exists as to the varieties, if any, of chronic Bright's disease and their relation to one another. The morbid appearances may

be further complicated by the possibility of attacks of acute or subacute nephritis supervening on chronic nephritis.

The differences in the appearances of the kidneys depend on the degree of change, on the one hand, in the epithelial structures, and, on the other hand, in the connective tissue. But although a tubal or parenchymatous or desquamative nephritis, that is to say, a kidney in which the main stress of the disease is in the tubal structures, may be recognised, yet even in the most extreme form of this disease there is some alteration of the connective tissue. In other instances in which the kidney is small and shrunken it would, from the large amount of connective tissue present, appear at first sight as if the main lesion were interstitial; careful examination, however, shews that much of the diminution in size is due to the shedding and disappearance of large areas of tubular epithelium, and that the large amount of fibrous tissue present is partly dependent on a relative rather than on an absolute increase. Great individual variations in the relative degree of the tubular and of the interstitial changes have led many authorities to the view that the one is a later stage of the other; and that in the earlier stages of the disease the lesions are mainly tubular, and that subsequently a more or less secondary and slow overgrowth of connective tissue takes place and leads to shrinkage of the organ. At one period it was even thought that the true granular kidney might arise in this way—in other words, that the true red granular kidney might be the final stage of a chronic parenchymatous tubal nephritis; and some even considered that the latter might in turn arise as a sequel of acute nephritis, and that therefore acute nephritis, chronic parenchymatous nephritis, and granular kidney might all be stages in the evolution of one and the same lesion. It is now, however, well recognised that the true granular kidney is an independent affection, and in no way to be looked upon as the final stage in the evolution of chronic nephritis, or at any rate of chronic tubal parenchymatous nephritis. This separation of the granular kidney from chronic parenchymatous nephritis is confirmed by the study of the clinical course of the disease, inasmuch as patients with granular kidney do not give a history of having previously suffered from dropsy and the other phenomena of chronic Bright's disease. Although the red granular kidney is now more associated with cardiovascular changes than with past attacks of chronic Bright's disease, yet many writers think that a certain form of fibrotic kidney presenting some points of resemblance to granular kidney may arise as the sequel of chronic tubal nephritis. To those holding these views the variations in the size of the kidney and the degree of fibrosis present would depend largely on the duration of the malady, although possibly in some instances the etiology of the disease, for instance when due to the virus of scarlet fever or to the action of such a poison as lead, might be a factor in determining the form of lesion present.

One of the principal difficulties in regarding all forms of renal fibrosis other than the granular kidney as the sequel of a former attack of

chronic tubular nephritis lies in the clinical histories of these cases. These contracted fibroid white kidneys are seen more especially in the young, or at any rate in young adults, and in a very large proportion of cases these patients give no history of any previous renal illness and certainly no history of an illness accompanied by dropsy. Although dropsy does not occur in all cases of chronic tubular nephritis, yet it is very general, and hence it is difficult to believe that the contracted white kidney is always the sequel of former chronic nephritis. Many of the patients dying from this disease give no history of any acute illness, and not uncommonly present no symptoms of ill-health until the onset of the terminal and fatal symptoms due to the renal lesion. These considerations make the etiology and the relation of this form of renal disease to other forms of nephritis exceedingly obscure, but at any rate it is probable, if not certain, that this form of chronic nephritis cannot be looked upon merely as the sequel of ordinary chronic nephritis. Although, as already stated, great individual differences are seen in the kidneys in cases of chronic Bright's disease, I am of opinion that two main varieties may be recognised, and that the differences between these two forms are not confined to their morbid anatomy, but may also be recognised in their symptoms and clinical course. The nomenclature of these conditions presents some difficulty, but probably the simplest plan is to speak of one as the large white kidney and of the other as the contracted or small white kidney.

Morbid Anatomy.—In the *large white kidney* the organs are increased in size, usually to a moderate amount, so that each organ weighs from 6 to 9 ounces. Its surface is smooth, and it may be white or yellowish-white in colour. Not uncommonly it is marbled and the veins on the surface are conspicuous. When the disease has run a rapid course there may be numerous red points due to dilated vessels or small haemorrhages; these latter appearances, however, are more often seen in the later stages of the acute nephritis than in the chronic form. The capsule strips off, leaving a smooth surface, and on section the cortex is seen to be considerably thickened and of a peculiar opaque yellowish-white colour. The portions of the cortex extending down between the pyramids are also increased in width, and the increased size of the kidney depends on this enlargement of the cortex. The pyramids are congested, and the line of demarcation between the cortical substance and the medulla is well marked. The cortical tubules are dilated and their cavities occupied by masses of desquamated and granular epithelium, the cells still adherent to the basement membrane often shewing hyaline and fatty changes. In many places the tubules may be destitute of cells which have been shed, and in other parts the epithelium may still appear normal, the incidence of the morbid process being unequal in different parts. The glomerular tuft shews a certain amount of cellular infiltration, and the epithelium lining the glomerular chamber has generally undergone proliferation, and masses of cells are often found filling up the gap in the glomerular chamber between the basement membrane and the capillary tufts. The walls of

the capillaries often shew signs of hyaline degeneration. The interstitial tissue usually presents some morbid appearance, in many instances an infiltration of young cells, and in cases of longer duration an overgrowth of fibrous tissue. The blood-vessels of the kidney usually also shew some evidence of peri- and end-arteritis, but in this form of the disease the tubular changes are the most prominent, the interstitial and arterial changes being far less obvious. Fatty metamorphosis may be present in very varying degrees, and is especially marked in those instances in which the kidneys are considerably increased in size and the surface distinctly yellow. The fatty change is especially marked in the epithelium of the convoluted tubules.

The lardaceous kidney is often large, pale yellow and waxy looking; in size it may equal or exceed that of the large white kidney. It differs from it in being firmer in texture and more translucent in appearance; but often there is a great resemblance in the naked-eye appearances of the conditions, and they can only be distinguished with certainty by the aid of the iodine test.

In the second variety of the affection, *the contracted white kidney*, the naked-eye appearance of the organs is very different. They are small in size, sometimes weighing no more than $1\frac{1}{2}$ to 3 ounces. The capsule is thickened, often to a considerable extent, and when stripped off leaves a uniform highly granular surface, the individual granulations often being of large size. Although the surface is highly granular the capsule is not always so adherent that its removal leads to tearing of the kidney substance. On section the cortex is greatly diminished in width, in places not being more than one-sixteenth of an inch thick; it is opaque, pale in colour, and the distinction between it and the medulla is obscured. The great diminution in the size of the kidney leads to an apparent increase in the amount of fat seen in the hilum. On microscopic examination it is seen that the tubules have in great part lost their epithelium, and where this change is well marked it may be difficult to recognise any characteristic renal structure. The loss of the epithelium is followed by the flattening of the tubules, and thus in many parts of the kidney no remains of convoluted tubules can be found, their place being taken by the overgrowth of interstitial fibrous tissue. In those parts where the tubular epithelium remains there are usually well-marked signs of hyaline degeneration, and the characteristic structure is therefore lost. The glomeruli are small and the walls of the glomerular chamber are greatly thickened from formation of fibrous tissue, with the result that the glomerular tuft is compressed and atrophied. The interstitial tissue is greatly increased in amount throughout the organ, although the increase may be greater in some parts of the kidney than in others. Here and there tubules lined with more or less normal epithelium may be found, and in other parts dilated tubules lined with a flattened epithelium are also seen. The diminution in the size of the kidney is mainly dependent on the disappearance of large numbers of the tubules, and is not entirely due to the atrophy caused by the overgrowth of the interstitial tissue. The

renal vessels shew well-marked peri- and end-arteritis, and the appearances of the kidney as a whole present considerable resemblance to those seen in granular kidney.

Although both the macroscopic and microscopic appearances in the large white and in the contracted kidney are very different, cases more or less intermediate between the two occur ; that is to say, cases in which the kidney is not so greatly diminished in size, and in which in addition to marked changes in the tubules similar to those seen in the large white kidney, there is also great overgrowth of the interstitial connective tissue. For this reason there is much to be said in favour of grouping all these various forms of nephritis under the heading of chronic diffuse nephritis, since all the elements of the kidney are affected to a greater or less extent in different instances. There does not seem to be any reason for thinking that these different forms pass into one another, although at first sight it might be thought that the small contracted white kidney was but a terminal stage of the large white kidney. This is highly improbable on clinical grounds, since in any given case the symptoms associated with the large white kidney are not known to precede those associated with the small white kidney. It is more probable that these different forms of chronic nephritis are distinct diseases evolving along their own special lines, and that in one case chronic nephritis takes the form described above as the large white kidney, and in another case takes the form described as the contracted or small white kidney.

Symptoms.—The initial symptoms of chronic Bright's disease are often insidious, and thus the malady does not attract notice until it has existed for some time. In the minority of cases the symptoms produced by acute nephritis merge into those due to the chronic disease ; but, as already mentioned, it is exceptional for chronic nephritis to supervene directly on the acute disease. In some instances, however, the onset of symptoms is so sudden as to suggest an acute disease, and yet the examination of the patient definitely shews that the disease has existed for some considerable time. In a remarkable group of cases in which the initial symptoms are of a uraemic character and in which the patient, who was apparently in good health previously, may die after a very short illness, the autopsy reveals advanced chronic renal disease. In some of these cases death has occurred after an illness of only a few days' duration, the first manifestation of the long existing renal disease being the onset of epileptiform seizures, or an attack of uraemic dyspnoea simulating asthma. In other instances in which an apparently sudden onset has occurred the symptoms have really been due to some complication, such as pericarditis. Still, notwithstanding these exceptions, the initial symptoms of chronic renal disease are in most cases vague and insidious. The most constant symptom is a general failure of health shewn by lack of energy, unnatural fatigue, loss of appetite, digestive disturbances, and possibly some loss of flesh. The loss of flesh is often much more marked in cases of the contracted kidney, and in some instances is so great as to arouse a suspicion of some form of deep-seated

malignant disease. Anaemia and its symptoms, such as breathlessness on exertion and palpitation, are very characteristic of chronic renal disease ; still, it must be remembered that the malady may exist even in an advanced form without the patient presenting obtrusive evidence of anaemia.

In a considerable proportion of cases dropsy is the first sign to attract attention, and the patient may first notice a feeling of unnatural heaviness of his legs, and then on examination he finds them to be swollen. The dropsy varies in its amount and also to some extent in its position ; the most characteristic form is that in the subcutaneous tissues, especially of the face, so that on waking in the morning the eyes are found to be baggy. In other cases the swelling first appears in the legs or in the scrotum, and sometimes its onset is so sudden and widespread that a considerable degree of ascites may be the initial manifestation. When there is a high degree of general dropsy anaemia is usually well marked, and the dropsy may be so great that the patient may be almost unrecognisable, and the skin of the extremities may crack and blebs form as the result of the extreme tension. This, however, is exceptional, and the dropsy even when pronounced is soft and boggy. In most instances in which dropsy is well marked the other symptoms of the illness are also well developed ; but very definite dropsy is occasionally seen without any apparent great interference with the general health, and such patients may express themselves as feeling but little inconvenienced in any way except by the degree of the swelling. Fluctuations in the amount of dropsy in chronic renal disease occur from time to time, but the condition on the whole is apt to be very persistent, and even in moderately favourable cases the dropsy is likely to last for many weeks or even months. It may, however, diminish, and ultimately disappear even after it has existed for many months.

Physical weakness is one of the most characteristic features of chronic Bright's disease, and although no doubt especially prominent in cases in which there is much nausea, vomiting, and diarrhoea, it may be present to a high degree in the absence of these other symptoms. In cases of long duration the physical weakness amounts to prostration and the patient becomes extremely listless and apathetic. The weakness is doubtless correlated with the anaemia, and also with the considerable wasting which occurs in renal disease but is so often completely masked by the dropsy. The subsidence of dropsy in a case of chronic renal disease will often reveal an astonishing amount of wasting which was quite unnoticed while the dropsy lasted. The body temperature in chronic renal disease is often subnormal ; but in cases of no great severity it is normal, and the occurrence of a notable fall in the body temperature rather suggests the onset of uraemic complications. Vomiting, and especially nausea, are extremely prominent and characteristic symptoms of chronic renal disease and may be so severe as greatly to interfere with the feeding of the patient. Nausea is generally accompanied with a dry, furred, and brown tongue, and these patients often complain bitterly of

an extremely offensive, sometimes even a faecal, taste in the mouth. The state of the mouth is largely answerable for the anorexia which is so characteristic of severe cases. The vomiting of chronic renal disease is especially associated with the sight or the taking of food, and it is not uncommon for all food to be from time to time immediately rejected by vomiting. The vomiting is accompanied by intense nausea, not uncommonly by headache. The more severe types of vomiting are especially characteristic of uraemia. In the milder cases in which the vomiting is occasional and related to food there is generally much flatulence and some pain and abdominal discomfort after meals. The state of the bowels is very variable, but in some instances diarrhoea is troublesome, more especially in uraemic cases, and diarrhoea in a still more marked form occurs in association with a form of ulcerative colitis sometimes seen in chronic renal disease. Headache may be severe, especially in cases with uraemia or with marked cardiovascular changes. Headache is perhaps more particularly associated with high blood-pressure and the secondary cardiovascular degenerations than with uraemia, although the two conditions may be associated in the same patient.

A moderate degree of pigmentation of the skin is not uncommon in chronic Bright's disease, more especially in those cases of contracted white kidney without dropsy. Sometimes the pigmentation of the skin is so dark as to resemble that seen in Addison's disease. Rashes, such as erythema, purpura, urticaria, pityriasis rubra, and in rare instances bullous eruptions may occur. Erythema, particularly in a diffuse form, sometimes occurs in uraemia. Purpura, especially on the legs, is more often seen in ordinary chronic Bright's disease. Haemorrhage from the nose and from other mucous surfaces, particularly the gums, is common, and from time to time severe forms of stomatitis may occur, usually in the form of ulcerative stomatitis, and the gums may become greatly swollen and haemorrhages take place into their substance with subsequent necrosis of the superjacent mucous membrane. In rare instances a gangrenous stomatitis occurs in the course of chronic renal disease, and there may be copious and even fatal haemorrhage from erosion of a large vessel.

The symptoms in the two main forms of chronic nephritis, the large white and the small contracted kidney, are necessarily to a great extent similar, but there are some differences, and very commonly these are sufficiently definite to enable a differential diagnosis to be made. Thus, dropsy is often absent in cases of contracted kidney, and there may never have been dropsy at any period of the illness. This is one of the leading points of distinction between the two affections. Further, the symptoms due to secondary cardiovascular changes are generally far more prominent in the contracted kidney, and such patients may suffer not only from severe headache connected with high arterial pressure, but also from cardiac symptoms, such as praecordial anxiety and palpitation. In some instances the cardiac enlargement leads to valvular defects, such as relative mitral stenosis with a distinct presystolic murmur as the

result of hypertrophy and dilatation of the left ventricle, or mitral regurgitation with oedema of the cardiac type especially marked in the lower limbs. Patients with contracted kidney are, however, especially prone to well-marked disturbance of nutrition, whilst great wasting and a high degree of anaemia are not uncommon. It is especially in these cases that albuminuric retinitis is apt to be well marked, and a considerable number of such patients seek advice on account of the headache or the general weakness, and the renal disease is detected as a result of examination of the fundus oculi. Albuminuric retinitis is one of the most characteristic features of this form of renal disease, and is met with more frequently than in the large white kidney cases (*vide* also p. 626). In a few exceptional instances profuse haematuria may occur from time to time, and when this is associated with extreme wasting and great impairment of physical strength, an erroneous diagnosis of malignant disease of the kidney has sometimes been made. A considerable proportion of the patients with contracted white kidneys are young, or, at any rate, young adults under 25 to 30 years of age. One of the most striking points about these cases is that very commonly the disease runs a latent course and that the patients only seek advice for terminal symptoms, especially those due to the onset of uraemia; in fact, some manifestation of uraemia is, perhaps, the most characteristic feature of this form of renal disease. In the large white kidney death not uncommonly occurs from some inflammatory complication, such as pneumonia, pleurisy, or pericarditis, or from the exhaustion associated with long-continued presence of extensive dropsy. In some instances uraemia, especially in a chronic or subacute form, may be present, and is especially apt to appear in the course of some inflammatory complication; but with the contracted kidney acute uraemia is extremely apt to arise, and sometimes with great suddenness at a time when the general condition of the patient has been such as to allow him to carry on his usual avocation. Although uraemia may occur in any form of acute or chronic renal disease it is especially associated with this variety of chronic Bright's disease.

The various forms of *uraemia* are recognised according to the severity and the character of the symptoms produced. In some instances most of the symptoms can be referred directly to disturbance of the nervous system, in others the symptoms are especially gastric or intestinal, and accordingly nervous and gastro-intestinal forms are sometimes recognised. The most convenient classification of uraemic phenomena is that based on the clinical course and degree of severity of the effects, namely, the acute, subacute, and chronic. The chronic form is associated especially with chronic renal disease and, perhaps, most of all with the large white kidney. Such patients suffer from nausea, vomiting, abdominal pain and discomfort, diarrhoea, itching of the skin, and frequently twitchings and spasmoid contractions of various muscles, especially the extensors of the wrist. Headache is also commonly included as a symptom of uraemia, but in not a few instances it is really in closer connexion with the

concomitant cardiovascular lesions. Disturbances of the respiratory rhythm are also frequent in chronic uraemia, and many such patients present well-marked Cheyne-Stokes breathing which may be present for many weeks or even months. Where the uraemic symptoms are pronounced the body temperature is apt to be low, and is often subnormal for prolonged periods. Chronic uraemia is usually also associated with the excretion of a scanty urine, and even in cases in which a moderate quantity is passed there may be much deficiency in the solids of the urine. Cutaneous eruptions, especially erythema, purpura, and bullae, are prone to occur in such cases.

In acute uraemia the symptoms are very much more severe, and in some instances the development of the uraemic state is so rapid and the symptoms are so severe that the term fulminating uraemia has been applied to them. Acute uraemia may not only complicate acute renal disease, but is especially apt to occur in cases of chronic Bright's disease with small white, and contracted kidneys. In rare cases the onset of acute uraemia may be the first intimation of the existence of renal disease; for instance, in a patient engaged in his usual avocations acute uraemia may appear with great suddenness and prove fatal within 48 hours. These cases present a considerable resemblance to the cases of acute acid intoxication in diabetes in that in both conditions a serious chronic disease may be present without any symptoms sufficient to attract the patient's attention, but may suddenly cause death from grave toxæmia. Extremely severe epileptiform seizures are amongst the most common manifestations of acute uraemia, but sometimes very severe, painful, and generalised cramp may usher in the attack, and cases have been described with spasms of a tonic or almost tetanic character. The epileptiform seizures of uraemia may begin locally, but they very soon become generalised, and they may be of such severity that the patient rapidly passes into the status epilepticus; unless they are comparatively slight consciousness is soon lost, although the degree of coma produced is rarely so deep as that seen in cerebral lesions, such as cerebral haemorrhage. When the fits are frequent and of great severity the body temperature may rise and hyperpyrexia may occur; but if the fits are slight and the drowsiness or coma marked, the temperature is more often normal or subnormal. In rare instances uraemia may be ushered in by paroxysmal and maniacal excitement; this, however, is unusual except in cases of chronic illness in which other symptoms of renal disease have been present, often for a considerable time. Drowsiness and coma are very constant manifestations of acute uraemia and are usually present in uraemia complicating chronic Bright's disease. Sudden amaurosis may be the first manifestation of uraemia, and in rare instances a sudden palsy, as, for instance, of one side of the face or of one limb, may appear without any gross lesion being found after death to account for this so-called uraemic palsy. Dyspnoea is, however, the most constant symptom of acute uraemia; most frequently it is of the hissing type described by Addison, and the respiratory movements may

be extremely laboured. The dyspnoea is usually associated with the presence of pulmonary oedema. Sometimes there is Cheyne-Stokes breathing, but perhaps more commonly there is a resemblance to the paroxysms of dyspnoea associated with asthma. Intense dyspnoea may be the only manifestation of acute uraemia, and in such instances it may be confounded with anaemia, or, if some inflammatory complication such as pericarditis be also present, the dyspnoea may be attributed to this when it is really an initial manifestation of uraemia. Hiccup may also be a prominent symptom and give rise to great distress. In a few exceptional instances the uraemic state is characterised by an extraordinary restlessness and sleeplessness instead of the usual drowsiness and coma, and patients have died with uraemic dyspnoea and restlessness without any drowsiness or coma. In very exceptional instances catalepsy may be present in uraemia.

In most cases of chronic renal disease the onset of uraemia is gradual, dyspnoea and drowsiness and stupor being the most common and constant initial symptoms. Sometimes, however, the onset is sudden, a series of epileptiform or eclamptic seizures taking place. The occurrence of uraemia in chronic renal disease is always a very serious complication, and the prognosis is very bad unless the uraemic manifestations are of a slight character. When acute nervous phenomena, such as fits, urgent dyspnoea, or coma, supervene in the course of chronic renal disease the outlook is exceedingly bad. There is a striking difference in the prognosis of the epileptiform or eclamptic seizures accompanying the nephritis of pregnancy and acute nephritis generally on the one hand, and the same seizures occurring in the course of chronic renal disease on the other hand. The prognosis in the latter cases is far more serious than in the former, and although temporary recovery may not uncommonly take place as the result of energetic treatment, the ultimate outlook is very grave. This is also necessarily the case when uraemia occurs in association with inflammatory complications such as pericarditis.

Secondary Inflammations.—Inflammations of the serous membranes, especially pericarditis and pleurisy, rarely peritonitis, occur with considerable frequency in all varieties of chronic renal disease. It was at one time supposed that these inflammatory complications were directly dependent on the presence in the blood of the toxic substances causing uraemia. Modern knowledge has shewn, however, that these inflammations have a microbic origin, and that in renal disease the resistance of the tissues to microbic infection is seriously diminished. Bronchitis and pneumonia are also common, and inflammatory conditions of the alimentary canal such as stomatitis, gastritis, entero-colitis, sometimes of the ulcerative form, also frequently occur. In almost all these affections the occurrence of the illness is very profoundly modified by the existence of the renal disease. Thus, the pericarditis of Bright's disease is apt to run an exceedingly unfavourable course, and death may ensue even when the pericarditis is not necessarily very extensive. Various forms of

pericarditis may occur ; not uncommonly the disease is latent and does not produce any very distinct symptoms, pain being absent, and the condition can only be recognised by the detection of physical signs, such as friction in dry pericarditis or friction followed by the signs of effusion in the other form of the affection. Dry pericarditis is not uncommon ; but pericarditis with effusion also occurs, and the effusion may be purulent. In some instances the effusion has been found to be sterile. Pleurisy, unilateral or bilateral, is a fairly common complication, and pneumonia is especially frequent. The pneumonia is very apt to take the form of a diffuse lobular pneumonia, the lung substance being imperfectly consolidated, semi-solid, and oedematous, and the physical signs are therefore often somewhat indefinite. Peritonitis and meningitis are also occasional complications in chronic renal disease, and in some instances peritonitis has arisen as the result of the perforation of stercoral or uraemic ulcers in the bowel (*vide Vol. III. p. 574.*)

The urine in chronic renal disease is usually pale in colour and of low specific gravity, and the quantity excreted depends very largely on the presence or absence of dropsy and on the form of renal disease present. In the more advanced cases of chronic renal disease the urine may approximate in colour to water. It must, however, be remembered that occasionally a dense urine may be excreted, especially in the cases of chronic Bright's disease complicated by cardiac dilatation and secondary cardiac failure, but with this exception, it is unusual to find the urine in chronic renal disease even approximately of the normal colour and specific gravity. In chronic nephritis accompanied by dropsy the urine is diminished to less than half the normal output and, not uncommonly, far smaller quantities than this are excreted ; thus, the daily amount may fall to between 10 and 20 ozs. Such a scanty excretion is usually associated with the onset of dropsy. Every fluctuation in the amount of dropsy is also marked in the daily urinary excretion, and the variations in the amount of urine often afford a more delicate indication of the progress and the course of the dropsy than observations on the amount of fluid present in the cavities of the body or in the subcutaneous tissues. The subsidence of the dropsy is always marked by a great and often sudden increase in the daily quantity of urine excreted. It must also be remembered that the kind of diet and the amount of fluid lost by other channels may greatly influence the daily output of urine. Thus, on a milk diet the urinary excretion may undergo a very considerable increase even in cases of chronic tubular nephritis in which normally the quantity excreted is less than 50 ozs. daily. Again, an attack of diarrhoea or free purging with salines may greatly diminish the daily output. In the cases without any dropsy, and more especially in cases of contracted white kidney, the daily excretion of urine is increased to a moderate extent, such as 50, 60, or 70 ozs. In exceptional instances even larger quantities rivalling those seen in the granular kidney and in the amyloid kidney may be excreted. Care must be taken always to ascertain that the increased excretion of urine is not dependent on a

milk diet before attributing it to the presence of contracted white kidney. The onset of uraemia, especially in chronic tubal nephritis, is often heralded by a diminution in the excretion of urine, but acute uraemia of the most severe form may occur in chronic renal disease at a time when quite considerable quantities of urine are being excreted, although such urine is often extremely dilute, of low specific gravity, and containing but few urinary solids. The percentage of albumin in the urine is usually considerable in all forms of chronic Bright's disease, except the true granular kidney, and in chronic tubal nephritis the deposit may amount to half or three-quarters of the volume of the fluid. In the contracted white kidney the amount of albumin is also large, but usually not so great as that seen in chronic tubal nephritis; at least the percentage is less, but the total amount of albumin lost in the 24 hours may be greater owing to the increased urinary excretion present. Variations in posture and in diet may lead to differences in the amount of albumin.

The quantity of urea excreted daily is generally much below the normal and may not amount to more than a third or half the normal, but it must be remembered that the appetite of these patients is often poor, that vomiting is not uncommonly present, and that a considerable amount of protein passes out in the urine as such. Casts are usually present, and the variety of cast will often give a clue to the nature of the renal lesion. Thus epithelial, granular, and fatty casts may be present in abundance in tubal nephritis, and granular and hyaline casts in cases of contracted white kidney.

Diagnosis.—Most cases of chronic nephritis present no great difficulty, in so far as recognising the presence of chronic renal disease, although it may be difficult and sometimes impossible to determine with certainty the particular form of renal lesion present. There are, however, some special diagnostic problems in some instances of chronic renal disease. In the first place, it may be difficult to decide absolutely whether there is chronic renal disease or whether there is simply so-called functional, physiological, or postural albuminuria. A still more difficult question which constantly arises is to ascertain with certainty whether albuminuria, usually slight in amount, is due to a chronic and progressive lesion, or is merely the relic of damage produced by a past attack of acute nephritis, and therefore non-progressive. Many authorities do not differentiate between these two conditions, and regard persistent albuminuria, especially if considerable, as unequivocal evidence of chronic nephritis. The distinction between a progressive and a non-progressive lesion is, however, a very real one, since in the latter case the albuminuria may exist for years without producing any serious results, the general health being maintained, and the patient presenting no signs or symptoms of illness other than the albuminuria. The separation of functional albuminuria must be made largely on the postural characteristics of the albuminuria and on the absence of other signs, especially cardiovascular changes and dropsy. Again, in some instances albuminuria may depend on a

contamination of the urine with small quantities of pus, due to irritation, for example, that caused by a stone ; and from imperfect examination of the urine the albumin is recognised, but not the pus, and the patient is erroneously supposed to be suffering from a chronic renal disease, a mistake which can be avoided by a thorough examination of the centrifuged urinary deposit.

In chronic tubal or parenchymatous nephritis dropsy is usually present, and enables these cases to be recognised easily. In the contracted white kidney, on the other hand, dropsy is usually absent ; and since the prominent symptoms are often those due to the disturbance of nutrition, loss of strength, wasting, and pigmentation, grave errors of diagnosis may arise unless the urine is examined. The low specific gravity of the urine and the considerable amount of albumin present, together with the changes in the fundus oculi and in the heart and arteries, usually render the recognition of the disease easy.

Considerable difficulties, however, may arise in the cases in which the first symptom of serious illness is the occurrence of some uraemic seizure, such as dyspnoea or epileptiform attacks. Thus, the dyspnoea may be regarded as due to asthma, and the albuminuria be erroneously explained as secondary to the dyspnoea, whereas the dyspnoea is in reality dependent on the renal lesion. In cases in which epileptiform seizures are prominent, there may be a further difficulty in diagnosis ; for it appears that in some rare cases of epilepsy the urine may not only be albuminous during and shortly after the seizure, but may remain albuminous for some days, so that when these patients are seen shortly after or during the epileptic paroxysm, it may be extremely difficult to determine whether the seizures depend on uraemia, or whether the albuminuria is due to the epileptic attack. In the great majority of instances in which uraemia suddenly complicates chronic renal disease, albuminuric retinitis is present, and affords a certain means of diagnosis ; but occasionally uraemia occurs and proves fatal in chronic renal disease without the presence of albuminuric retinitis. This, however, is rare, especially in the contracted white kidney in which dropsy is absent ; but it is precisely in these cases that the difficulties of diagnosis are greatest. The history of the patient and the course of the illness may ultimately afford a means of accurate diagnosis, since the acute uraemia of an epileptiform character occurring in association with the contracted white kidney is usually fatal ; whereas epileptics with definite albuminuria may have a succession of such attacks spreading over many years.

Prognosis.—Patients with chronic Bright's disease often live for many years with comparatively little discomfort ; and instances are seen from time to time in which an albuminuria of thirty to forty years' duration has dated from nephritis associated with dropsy. The prognosis mainly depends on the form of renal disease, and the presence or absence of complications. Thus, in the contracted white kidney life is not maintained for any considerable period, and the large proportion of cases die within a few weeks or months of its recognition, although doubtless it

has existed for a considerable time before the onset of symptoms. The presence or absence of retinal changes is extremely important from a prognostic point of view, for it is exceptional for patients with albuminuric retinitis to live beyond a year from the time of the detection of the retinal changes (*vide* p. 626). In chronic tubal nephritis the prognosis depends largely on the presence or absence of persistent dropsy, and on the degree of anaemia present; both of these signs are unfavourable. In both forms of chronic nephritis, when the disease is sufficiently severe to have produced symptoms, life is very uncertain, more especially because it is impossible to foresee the occurrence of some secondary inflammation, of acute uraemia, or of cerebral haemorrhage; but in cases in which albuminuric retinitis is not present, and in which the cardiovascular changes are slight, and the general nutrition of the patient not profoundly affected, life may be maintained for many years, and, as already stated, such patients may suffer very little discomfort. The onset of acute uraemia is an exceedingly unfavourable sign; in chronic tubal nephritis, subacute or chronic uraemia may be present for some months, but acute uraemia is commonly rapidly fatal.

The prognosis of the nephritis of pregnancy is more favourable than that of other forms of the disease, inasmuch as even such serious symptoms as considerable dropsy and eclampsia may subside and the albuminuria disappear within a short time of the emptying of the uterus. Even in the presence of albuminuric retinitis the prognosis is not so unfavourable as in other forms of albuminuric retinitis, and these patients may live for a considerably longer period than is the case with other varieties of chronic Bright's disease (*vide* also p. 603).

Treatment.—In some instances the dietetic treatment of chronic Bright's disease must be conducted on similar lines to that of acute nephritis. This is more especially the case when uraemic symptoms are present, but in the majority of cases the extreme restriction of diet advisable in acute nephritis is not suitable for the chronic disease. Certainly the diet should not be determined merely by considerations of the state of the urine, and more especially the amount of albumin present. A wider view should be taken, and the general state of the nutrition of the patient, and also his feelings of well-being or the reverse should all be considered. It may sometimes be advisable to restrict these cases to a diet of milk thickened with some farinaceous materials for a considerable period; but it must be recognised that such a rigid dietary as this is not always advisable, and that in not a few cases it may be distinctly prejudicial, inasmuch as the general health is lowered, without any notable improvement occurring in the renal lesion. Formerly it was not uncommon to keep patients with chronic Bright's disease on a rigid milk diet for months, as it was thought that the albuminuria could in this way be checked. It is, however, very difficult for the adult to maintain the general nutrition in a satisfactory state on a pure milk diet; and, further, in cases in which dropsy is a prominent feature, it is probable that the large quantities of fluid necessarily taken in the milk diet

are prejudicial to the subsidence of the dropsy. Many authors also consider that milk is too rich in saline constituents, especially sodium chloride, and that this also may aggravate and tend to maintain the anasarca. Thus in most cases probably the best course to follow, at any rate in the presence of any urgent symptoms, such as dropsy or uraemia, is for the patient to be kept in bed on a diet of milk, farinaceous foods, and fruit. If signs of improvement manifest themselves, this diet may be continued; but if, as is often the case, no material change takes place, either in the general condition or in the state of the urine, there is probably little to be gained by persisting in such a diet for prolonged periods. More benefit may result from a drier diet, and one containing a considerable quantity of vegetable matter. When dropsy is a prominent feature there can be no doubt that, in some instances at any rate, considerable improvement may ensue from removing chlorides as far as possible from the food.

In cases of long standing in which anaemia is very frequently a striking feature, and the general condition of nutrition is poor, it is advisable to relax the diet further, and to allow meat, poultry, and fish in small quantities. The general tendency is to order fish and poultry rather than red meat; and very frequently this is beneficial, inasmuch as fish and poultry are more readily digestible, the digestibility of the various articles of diet being a very important consideration in such cases.

It is obvious that all patients with chronic renal disease should reduce the nitrogenous ingesta as much as possible; but it is essential not to reduce the food, even the protein food, to such an extent as to compromise the general nutrition; and further, it must be remembered that a considerable loss of albumin is present in renal disease, and thus a diet that increases somewhat the albuminuria may yet be beneficial, as the increased albuminuria may be small in proportion to the total amount of protein ingested. In other words, a patient who has been taken off a milk diet and put on one containing meat may perhaps excrete slightly more albumin in the urine; but this increased loss is more than made up for by the far larger quantity that is metabolised and utilised by the tissues. All writers are agreed that meat extracts, strong animal soups, concentrated meats, such as preserved and smoked meats, are unsuitable articles of diet, and further, that great care should be taken that all food is fresh and simply and plainly prepared. The use of alcohol is inadvisable in chronic renal disease, but not uncommonly the patients find it difficult to take sufficient food without the help of alcohol. If it be ordered, care should always be taken that as little as possible be given, and that it is taken in a freely diluted form.

The dropsy of chronic renal disease must be treated on the same lines as in the acute, but there is not the same theoretical objection to the use of diuretics in the chronic disease, and digitalis and caffeine as well as simple diuretics like the acetates and citrates may be very useful. Tonics such as iron, strychnine, and arsenic, more especially iron, are often of great value, as the degree of anaemia may be considerable.

III. GRANULAR KIDNEY

SYNOMYS.—*Chronic Interstitial Nephritis ; Contracting Granular Kidney ; Gouty Kidney ; Fibrosis of Kidney.*

Morbid Anatomy.—The true granular kidney possesses some points of resemblance in its morbid anatomy to the form described as the contracted white kidney (*vide p. 611*). Both shew great overgrowth of interstitial connective tissue and prominent arterial lesions which, however, reach a higher grade in the granular kidney than in the contracted white kidney. Further, in the granular kidney the arterial changes are much more widespread in the vessels generally and are advanced elsewhere than in the kidneys. Further, in the granular kidney the epithelial changes in the tubules vary greatly. In the earlier stages they are extremely slight, whereas the interstitial and vascular lesions may be already considerable. In the contracted white kidney, on the other hand, the lesions in the tubules are always well marked, and, in fact, the prominent feature of the disease is the great destruction of the renal epithelium. In the true granular kidney this is only seen in advanced and late stages of the disease. The granular kidney is especially prevalent in the latter half of life, and its occurrence before forty years of age is uncommon although not unknown ; the contracted kidney, on the other hand, is more especially seen in the young ; although, therefore, there may be some resemblance between the histological appearances of the granular kidney and of the contracted white kidney, the two affections must be regarded as distinct.

Several forms of the true granular kidney may be differentiated, depending on variations in the degree of the renal lesion and of the generalised arterial lesions. In some instances at the time of death arterial sclerosis may have reached a high grade in the body generally, but the degeneration of the renal elements may not have advanced very far, whilst in other instances the renal changes have reached a higher degree of development and have led to great atrophy of the kidney substance. Thus, in some instances the kidneys are found to be large or of normal size, in others shrunken and greatly atrophied. It has therefore been suggested that there are two forms of the disease—one primarily renal, and a second in which the renal changes are only consecutive to general widespread arterial sclerosis. There can be no doubt about the close association of arteriosclerosis and granular kidney ; those who regard the arteriosclerosis as secondary to the renal disease consider that the latter leads to high blood-pressure as a result of the presence of some toxic material in the blood which either acts on the vasmotor centre or, possibly, directly on the muscular coat of the arterioles. The increased blood-pressure ultimately leads to the

production of arteriosclerosis. On the other hand, in the other form of granular kidney accompanying arteriosclerosis the lesions in the arterial system lead to a considerable impediment to the freedom of the circulation through the kidney and other organs, and the impaired nutrition brought about as a result of the arterial obstruction is thought to be sufficient to account for the degeneration of the renal elements and the subsequent overgrowth of fibrous tissue.

Experimental destruction of the renal epithelium by the injection of small quantities of bichromate of potassium into the renal artery is not followed by the development of fibrous tissue in the interstitial connective tissue of the kidney. It is possible, by injecting small quantities of bichromate of potassium directly into the renal artery on one side, to destroy the whole of the epithelium of the tubules of that kidney without producing any very marked effect on the renal epithelium of the opposite kidney; hence life may be maintained; and in these instances, although the kidney on the side on which the injection has been made becomes atrophied and the epithelium shed, there is no overgrowth of fibrous tissue. It is probable that in order to lead to the fibrous over-growth the action of the toxic agent must be slow and continuous, and that the mere destruction of the higher elements by the sudden action of a toxin is not sufficient to lead to fibrosis. There are difficulties in the way of regarding arteriosclerosis as necessarily the result of the renal lesion, and also in looking upon the renal lesion as necessarily the result of arteriosclerosis, and it may well be that both these phenomena are really the result of the direct action of toxic substances on the kidney in the one case and on the vessels in the other.

The kidneys in granular kidney vary much in size, and may weigh as much as 6 ozs. or as little as $1\frac{1}{2}$ oz. In the very early stages the capsule is not adherent, and the surface is smooth and shews no change to the naked eye; but on microscopic examination the interstitial connective tissue is thicker than normal, and the increase is most marked in the cortex round the blood-vessels. Here and there degenerated Malpighian bodies may be found, there is endarteritis, and, according to Dr. Herringham, the muscular coat of the vessels may shew distinct evidence of atrophy. In more advanced cases the capsule is adherent, and on stripping tears the cortical substance; the surface of the organ is distinctly rough and granular, and frequently numbers of small cysts of varying size are seen. The surface of the kidney may be of a deep red colour, with well-marked granulations giving rise to the term raspberry kidney. In other instances the surface is mottled; the cortex is greatly diminished in width, measuring sometimes not more than $\frac{1}{8}$ th of an inch. On section the kidney is tough and the vessels stand out prominently, their walls being greatly thickened, and this thickening frequently occupies a portion only of the circumference so that the cavity of the vessel is irregular on section. The connective tissue of the kidney generally is enormously increased in amount but not necessarily uniformly. In some portions of the section the place of kidney tissue is entirely

taken by masses of fibrous tissue. The overgrowth of connective tissue is most marked in the cortex and especially round the glomeruli; and many of the glomeruli are completely destroyed, having undergone atrophy; the capsules of the existing glomeruli are greatly thickened and surrounded by fibrous tissue, and they contain the remains of the capillary tufts which have undergone hyaline degeneration. Comparatively normal glomeruli may be found scattered here and there, but even in these the glomerular tuft usually shews some signs of thickening. The tubules present a number of changes; in many parts they are dilated and lined by hyaline cells. In other parts the tubules are dilated to form small cysts; in others the epithelium has undergone granular and fatty degeneration. When the kidneys are small large numbers of tubules are represented simply by their basement membranes. The arteries of the kidney shew very extensive changes; the intima is greatly thickened and fibrous, and the subendothelial layer also may increase in thickness to an extent equal to that of the other coats of the artery. The middle coat may also be thickened as the result of the formation of connective tissue, but it is often atrophic; there is often, in addition, a considerable amount of periarteritis. Thrombosis of the small interlobular arteries sometimes occurs.

Symptoms.—In cases of true granular kidney the symptoms, at any rate in the early stage, are much more indefinite in character than in the other forms of chronic Bright's disease. This is very largely because cardiovascular changes form such an essential part of the clinical picture in granular kidney. In some instances the symptoms may be definitely referred to the renal lesion, and this is more especially the case where the cardiovascular changes are not so prominent. As already mentioned, at least two forms of this disease may be recognised—one with widespread arterial sclerosis in which the renal lesion, although well-marked, has not reached a very high grade, and the other in which the degeneration and fibrosis of the kidney are extremely advanced whilst the general arteriosclerotic changes may be less marked. In the first category the patient's symptoms are apt to depend directly on the cardiac changes, the hypertrophy and dilatation, or on the results of the arterial lesions, such as cerebral or retinal haemorrhage. In the second category, in which the renal lesion is more advanced, the symptoms may more closely resemble those seen in chronic Bright's disease; thus, these patients commonly complain of the loss of physical energy, and very frequently present well-marked emaciation, and, further, definitely renal symptoms, such as nausea, loss of appetite, and vomiting, may be present.

The majority of cases of granular kidney are seen in middle-aged or elderly patients, especially men, and in the bulk of these cases the initial symptoms are generally cardiac, such as breathlessness and palpitation on exertion. Such patients often present the aspect of apparently rude health; the closer inspection of the face, however, often shews that the ruddy complexion is associated with slight cyanosis and dilated venules. The breathlessness and palpitation are not only increased by

exertion but may also be aggravated by the recumbent posture, and thus cause considerable interference with sleep. On examination the heart is found to be large, although the great increase in the size of the heart is sometimes masked by the presence of emphysema. Examination of the pulse shews the vessels to be thickened, and the blood-pressure is often extremely high, reaching 180 or 200 mm. of mercury. The blood-pressure, however, is not always markedly increased, and when the cardiac symptoms are especially prominent, as the result of cardiac dilatation, the pressure may be low or within the limits of health notwithstanding very definite thickening of the vessels. Many of these patients may suffer from severe headache, more especially when the blood-pressure is high. In other and more advanced cases the patients may present all the symptoms of mitral regurgitation, the cardiac rhythm being rapid and irregular, and oedema of the legs may be present to a varying extent. In not a few cases the first symptom to attract attention is the sudden occurrence of extreme tachycardia with or without cardiac irregularity. These cases of extreme tachycardia associated with cardiac hypertrophy, granular kidney, and arteriosclerosis are of considerable interest from the remarkably sudden onset of the tachycardia, and, further, because there may sometimes be very extreme tachycardia with comparatively little distress. In the cases with marked cardiac dilatation and oedema of the legs, the clinical picture so closely resembles that of mitral disease of valvular origin that it is often extremely difficult to determine whether a patient seen for the first time is really suffering from a primary valvular lesion with secondary engorgement of the kidney, or a primary renal disease with secondary cardiac dilatation. The state of the urine, especially its specific gravity, and the condition of the vessels of the body generally, but more especially those of the fundus oculi, usually afford the most accurate means of differentiating between the two conditions. In a considerable proportion of cases of arteriosclerosis and granular kidney the first symptom to attract the patient's attention is the impairment of vision from the occurrence of retinal haemorrhages. This serious complication is perhaps most apt to occur in the cases with well-marked arteriosclerosis, and perhaps points more to widespread arterial degeneration than to renal disease. Nevertheless, albuminuric retinitis and retinal haemorrhage are not infrequent in cases in which the renal lesion is severe and the arterial changes less marked.

Albuminuric retinitis is very common in renal disease, more especially in chronic renal disease, and it is peculiarly associated with those forms of chronic nephritis characterised by considerable overgrowth of fibrous tissue in the kidney; in other words, it is especially associated with interstitial nephritis in the form of the granular kidney and the contracted white kidney. Mr. Nettleship has made a very complete study of the association of retinal changes with renal disease, and although in the great bulk of cases albuminuric retinitis is especially associated with chronic interstitial and chronic parenchymatous nephritis, a few cases have been recorded in which it occurs in association with lardaceous disease

and even with secondary nephritis dependent on disease of the bladder or of the renal pelvis. Thus, Mr. Nettleship records three cases of albuminuric retinitis in association with chronic nephritis, due in one case to stone and in two others to cystitis following either stricture or enlarged prostate. The retinitis of chronic renal disease is more often seen in males than in females, in the proportion of 64 to 36 per cent (Nettleship). This incidence coincides very closely with the usual incidence of renal disease in the two sexes. In about two-thirds of the cases the patients' ages varied between 30 and 60 years, and more of the cases of albuminuric retinitis occurred in the decade from 50 to 60 than in any other. Hyaline thickening of the walls of the retinal vessels may be seen in the absence of albuminuria, and in young subjects this combination may justify the suspicion of the existence of granular kidney in an early stage. Thickening of the retinal arteries, however, is not so certain a sign of granular kidney in the absence of albuminuria in adults. In exceptional instances hyaline thickening of the retinal vessels together with retinal haemorrhages and white patches may be present in the fundus without any albuminuria. Retinal changes are not only present in association with renal lesions in adults, but also are frequently seen in the nephritis of the young. Albuminuric retinitis is far more frequently seen in association with interstitial nephritis in the young than in the cases of so-called parenchymatous nephritis. In a series of 80 cases of interstitial nephritis in the young observed by Mr. Nettleship, retinitis or multiple retinal haemorrhage was found in 31, in 10 cases the eyes were found normal, and in the remainder no ophthalmoscopic examination was made. In 43 out of 149 cases of parenchymatous nephritis the eyes were examined and found normal; in 7 cases retinitis was observed, and in the remaining cases no examination was made. It would seem from these statistics that retinitis was far more frequently present in the interstitial nephritis of the young than in cases of parenchymatous nephritis, although it is possible that the apparent excessive incidence is dependent on the eyes being more often examined in the one series than in the other. The retinal changes are very often extremely severe in the nephritis of the young, and the prognosis of these cases is exceedingly grave. Thus, out of 40 patients in whom retinitis was present death occurred in 16 instances in less than four months from the time when the retinal changes were first detected, and in only one case was life prolonged for as long as three and a half years. Interstitial nephritis in childhood and in the young is more common in females than in males. Thus, in Mr. Nettleship's series, in 51 cases of interstitial nephritis under 13 years of age 30 per cent were male and 70 per cent female; and thus albuminuric retinitis, like interstitial keratitis, is more apt to be seen in girls than in boys. In this respect there is a striking contrast to what obtains in adults, in whom both the incidence of renal disease and of albuminuric retinitis is far greater in the male than in the female in the proportion of two to one. Although albuminuric retinitis may exist in different degrees of severity in different renal affections, it does not seem

as if any special form can be correlated with special varieties of renal disease. The incidence of albuminuric retinitis would seem to be associated mainly with two factors, the blood state and the degree and extent of the arterial lesions present. Uraemia is peculiarly associated with albuminuric retinitis, so that it is uncommon for a high degree of uraemia to exist in the absence of ocular changes except when acute uraemia occurs as a complication of acute nephritis. Albuminuric retinitis is therefore of great diagnostic significance as not only indicating the presence of chronic renal disease, but also as giving information as to the nature of the renal lesion, inasmuch as it is far more common in the interstitial than in the parenchymatous variety; and further, it is of great prognostic significance, as prolonged survival is very improbable in the presence of albuminuric retinitis, death often occurring within a few months of the time when the ocular changes are first detected. It would seem, however, as already stated, that the prognosis is not so grave in the albuminuric retinitis of pregnancy. In this respect the retinal lesions resemble the renal lesions as the albuminuria of pregnancy, even when severe and when accompanied by other signs of renal disease, such as dropsy, may clear up and the patient may regain her former health.

Haemorrhage may occur from the nose, from the kidney or renal pelvis, leading to profuse haematuria, and, most important of all, in the brain. From the lowering of the blood-pressure, the epistaxis not uncommonly produces considerable relief, the headache and sleeplessness so often associated with high arterial blood-pressure thus improving. Cerebral haemorrhage in cases of granular kidney is extremely serious and not uncommonly fatal, the haemorrhage being very profuse as a result of the high blood-pressure. Haemoptysis has also been described in granular kidney, and has been attributed to the high blood-pressure and associated degeneration of the pulmonary vessels as well as to the vascular changes in the vessels of the lung that occur in emphysema, which is such a usual accompaniment of granular kidney.

In some instances uraemic symptoms and even acute uraemia may be the first intimation of the existence of granular kidney, and in others some inflammatory complication such as pericarditis may first attract attention to the underlying disease. In some rare cases granular kidney may reach a high grade, and even cause death without the occurrence of any general cardiovascular degeneration; these patients usually present symptoms of a renal type, more especially grave disturbances of nutrition with much wasting and vomiting, and subsequently uraemia is prone to supervene and to be fatal.

The urine in granular kidney is abundant, pale, and of low specific gravity; the quantity is usually in very considerable excess of the normal 50 oz., and commonly amounts to 70 or 100 oz. The increased quantity leads to frequency of micturition, especially at night, thus causing considerable interference with sleep. A small quantity of albumin is usually present, but the degree of albuminuria varies some-

what, and it is not uncommon for the merest trace only of albumin to be present. The albuminuria is considerably influenced by posture, and the urine passed on rising in the morning may be free from albumin, and thus such cases may present considerable resemblance to cases of postural or orthostatic albuminuria. The two conditions, however, can generally be differentiated by means of the other characters of the urine, especially the low specific gravity and the increased quantity present in granular kidney. Still, granular kidney cannot be excluded in any given instance merely on the ground that albumin is absent on a single occasion. Further, in exceptional instances albumin may be absent from the urine for a considerable period, and cases have been recorded from time to time in which granular kidney in an advanced stage has been present and in which death has resulted from uraemia, and yet the examination of the urine has failed to reveal the presence of albumin. In the early stages of the disease, and particularly in the form in which arteriosclerosis is well marked and the cause of the renal change, it is not surprising that albumin may be absent; the absence of albuminuria is more difficult to explain in the rare instances of the more advanced disease. The lesion, however, has a very irregular distribution in the kidney, and may cause complete destruction of some portions of the organ and yet leave others comparatively healthy; this is probably the explanation of the scanty, or even absence of, albuminuria. In cases with cardiac dilatation in which the clinical picture resembles that of mitral regurgitation, the degree of albuminuria may be greater, and such patients may often pass smaller quantities of urine on account of the presence of cardiac dropsy, especially in the lower extremities. Even under these conditions, if the renal lesion be at all advanced the urine will still be pale and of low specific gravity, and present very striking differences from the concentrated and albuminous urine excreted by the engorged kidney associated with primary mitral regurgitation.

Casts, especially hyaline casts and scanty granular casts, are generally present in the urine of granular kidney, and the hyaline casts may be found in great abundance. The deposit from the urine often contains in addition cells from the renal pelvis, leucocytes, and not uncommonly a few red blood-corpuscles. In exceptional instances considerable quantities of blood may be present as the result of haemorrhage from the kidney, or more probably from the renal pelvis, and in very exceptional instances the quantity of blood is sufficiently large to colour the urine uniformly deep red. Subacute nephritis may occur as a complication in some instances of granular kidney, and so cause a more intense albuminuria with the presence of epithelial and granular casts in abundance. The onset of uraemia is often accompanied by a diminution in the output of urine, but as mentioned above fatal uraemia may occur in granular kidney without any very great diminution in the daily output of urine. Such urine, however, on account of its low specific gravity, contains but little solid matter, few salts, and a low percentage of urea. The urine of granular kidney is often prone to deposit appreciable

quantities of uric acid either spontaneously while the urine is still in the bladder or else shortly after its expulsion. The presence of only a small proportion of salts and the scanty pigment are usually regarded as the causes of the precipitation of uric acid as such, and granular kidney may not only be associated with gout but also with gravel, although it is not necessarily nor invariably an accompaniment of either condition. Many writers, however, have supposed that the granular kidney eliminates uric acid very imperfectly, and deposits of urates are not uncommonly found in some varieties of granular kidney both in the renal tubules and more especially in the intertubular connective tissue.

Albumoses, sometimes in considerable quantity, may be found in the urine of cases of granular kidney; no very special significance can be attached to minute traces, but when large amounts are present it would seem that the albumosuria really depends upon the presence of bone disease and especially of multiple myeloma, and that the association of albumosuria and granular kidney is accidental and due to coexistence of the two diseases, myeloma and granular kidney, in the same patient.

Diagnosis.—The recognition of granular kidney is usually based on the presence of a dilute and slightly albuminous urine, together with signs of cardiac hypertrophy and arterial degeneration. In some cases the albuminuria is not only scanty but variable, and thus difficulties may arise in the recognition of the condition unless the urine be tested on several occasions. Further, it is not uncommon for the albuminuria to be of the postural type and the albumin to be either very scanty or absent in the urine passed on first rising in the morning.

In exceptional instances granular kidney may occur not only in young adults but even in children, and in these rare cases some difficulty may be experienced in distinguishing between postural or functional albuminuria and granular kidney. The presence of cardiovascular changes usually affords a means of distinguishing between the two conditions. Difficulties may also arise in the diagnosis of cases with secondary cardiac dilatation and the general features of mitral regurgitation. It is not uncommon in such instances for the presence of granular kidney to be revealed in the post-mortem room, the case during life having been regarded as primarily cardiac. In these cases also the state of the arteries, the colour and specific gravity of the urine, and the condition of the fundus oculi afford the best means of recognising the disease.

In a considerable proportion of cases cerebral haemorrhage is the first indication of the existence of the underlying disease, and granular kidney should always be looked for in cases of cerebral haemorrhage of a severe type. Both cerebral and retinal haemorrhages may occur as part of widespread arterial degeneration without there being necessarily any serious renal fibrosis. Neurasthenic symptoms may be the leading symptoms for which some patients with granular kidney seek advice, and the condition may be overlooked unless the urine be examined as a routine in all cases.

The prognosis is most uncertain, because it is always possible that

cerebral haemorrhage, uraemia, or secondary inflammations may supervene. Here also the prognosis depends largely on the degree of cardiovascular degeneration present, and on the extent to which the general nutrition has been impaired. A considerable proportion of these patients seem at first sight to be but little ill, and their main danger lies in the effects of high arterial blood-pressure, tending on the one hand to produce cerebral haemorrhage and on the other hand cardiac dilatation. Signs pointing to cardiac failure, such as marked dyspnoea on exertion or oedema of the legs, are unfavourable, inasmuch as the cardiac failure is very often extremely refractory to treatment. The onset of acute uraemia is also exceedingly unfavourable.

In the treatment of granular kidney much the same dietetic principles are involved as in the other forms of renal disease; but as the malady is extremely chronic better results are usually attained by a moderate diminution in the nitrogenous constituents of the food than by ordering any very rigid diet. Patients suffering from this affection have often been very large eaters, and especially large meat eaters, and they are intolerant of severe restriction, such as complete abstinence from meat. This is usually unnecessary unless complications are present, but the quantity of food should be diminished even in cases without symptoms, and meat should be taken once a day only and in small quantities.

Careful attention should be paid to the circulation, as the patients are exposed to grave risks as a result of the cardiovascular changes. If the blood-pressure is unduly high attempts should be made to lower this by restrictions in the diet, by free purgation with salines, and by the administration of vaso-dilator and other drugs. In some instances much benefit is derived from the use of vaso-dilators such as erythrol tetranitrate, which acts more slowly and less vigorously than either nitro-glycerin or amyl-nitrite. Further, patients should be warned of the risk of severe exercise and overstrain of all kinds. If care be taken with reference to the diet, the regulation of the arterial blood-pressure, and avoidance of strain and over-anxiety, patients may suffer comparatively little inconvenience from the morbid process for prolonged periods. In many cases of granular kidney the arterial pressure may, from progressive cardiac dilatation, have fallen to a level too low for the physiological needs of the individual; in such patients much benefit may be derived from the use of cardiac tonics, especially digitalis, both the breathlessness and the cardiac dyspnoea that is liable to occur in these cases being relieved by this drug. When cardiac dilatation begins to manifest itself either by signs or symptoms the patient should be kept at rest.

Sleeplessness is often difficult to treat in chronic renal disease, as it is very frequently cardiac, although sometimes it may be dependent on the toxæmia. Paraldehyde is often useful although its taste is very unpleasant, but in many cases nothing but small doses of morphine or opium will relieve the great distress from which the patient suffers; many authorities consider that the use of this drug is dangerous, and it certainly is so in the presence of pulmonary complications. The danger

of the use of morphine in renal disease has, however, probably been exaggerated. Chloral is often of great use for the relief of the restlessness and sleeplessness of renal disease, more especially in cases with high blood-pressure, as the drug produces considerable lowering of blood-pressure by its action on the vasomotor system.

Decapsulation has been strongly recommended by Edebohls as a method of treatment in chronic nephritis, but this procedure has not met with general acceptance, and in my opinion is not advisable.

Patients with all forms of chronic renal disease should if possible winter in a warm, dry, equable climate, but it is inadvisable to send cases abroad when symptoms of uraemia are present, even if they are only slight, as the fatigue and discomforts of travelling may precipitate the onset of acute uraemia.

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NEPHROPTOSIS

(MOVABLE OR FLOATING KIDNEY)

By Prof. ALEXANDER MACALISTER, M.D., F.R.S.

Definition.—The kidney is said to be pathologically movable when by pressure, by alteration in posture, or by changes in the distension of the surrounding parts, it undergoes displacement from the position which it usually occupies. This condition must not be confounded with congenital dystopia, in which the organ occupies a fixed position other than that of the normal kidney (*vide p. 645*).

Normal Position.—There is a considerable variation in the normal site of the kidneys as observed in different individuals; but, in general, the inferior pole of the right kidney is opposite a spot 3 cm. above a point 7 cm. from the linea alba on the horizontal line drawn through the umbilicus. The level of the superior pole is marked by a point 5 cm. from the linea alba on a horizontal line drawn on the abdominal wall 10 cm. above the horizontal umbilical line. The axis of the kidney corresponds to the line which joins these poles, and its hilum is on a plane internal to and below the edge of the eighth costal cartilage opposite the middle two-fourths of the axial line. The organ thus lies at the meeting-place of the hypochondriac, right lumbar, and epigastric regions as these are ordinarily defined. On the posterior wall of the abdomen the upper pole of the right kidney is 5 cm. external to the tip of the eleventh thoracic spine, and its lower pole is at a point 3 cm. above the iliac crest and 7 cm. external to the medio-dorsal line. The left kidney usually lies 1 cm. higher; and on each side the back of the kidney crosses the twelfth rib (*vide also Vol. III. p. 864*).

The kidneys are kept in their places to some extent by the pressure of the surrounding viscera under the constraint of the muscles of the abdomen. Schatz made the first formal attempt to demonstrate the existence of this constraining influence, and its amount was calculated by Haughton; but, on account of the insufficiency of the experimental data employed, the results arrived at are not of practical value. Weisker (159) has demonstrated experimentally that the intra-abdominal pressure in the sense of a retentive force is much less than Schatz supposed. The viscera during life are soft and plastic; and, as they are closely packed together, they exercise, by their mere weight, a certain amount of pressure the one against the other; so that when hardened *in situ* they are mutually faceted on their planes of contact. The disposition of the parts of the abdominal wall which lie dorsally and inferiorly to each kidney is such that when the kidney is carefully removed there is displayed a "kidney bed" for its reception. This bed is usually a well-

defined and fairly deep fossa in the male, but is shallower in the female, especially on the right side. The mutual pressure of the viscera and the tonic tension of the abdominal wall are sufficient to keep the normal kidney in its bed when this fossa is well marked. The right kidney has in front of it the right lobe of the liver and the duodenum; the left kidney is similarly compressed on its ventral surface by the spleen and stomach above, by the pancreas medially, and by the jejunum and (to a small extent externally) the descending colon below.

The adipose capsule acts as a pad around the organ, and has a basis of rather firm connective tissue continuous inwards behind the kidney with the subperitoneal tissue around the aorta. A layer of areolar tissue continuous with the capsule below can be traced upwards over the ventral face of the kidney to join the subperitoneal layer on the diaphragm above. On the left side this layer is thicker than on the right (Zuckerndl, Tolt). The tissue of the adipose capsule becomes filled with fat about the tenth year, more especially behind, below, and external to the gland. This fat is softer during life than it appears to be in the post-mortem room, and, as a retentive apparatus, the adipose capsule is important chiefly by contributing to make the kidney bed: a good description of the kidney bed is given by Wolkoff and Delitzin.

The peritoneal reflexions, on the front of the kidney, act as important factors in the fixation of these organs. On the front of the right kidney the serous membrane is reflected from each side of the ascending colon; on the front of the left kidney the serous reflexions from the upper and lower borders of the pancreas have a more definitely retaining influence. These attachments taken together, peritoneal and subperitoneal, are in general sufficiently strong to retain the kidneys in place in an opened abdomen when the cadaver is raised to the erect posture; and in only four out of twenty experiments did they permit of displacement from gravity. Wolkoff records a greater frequency of displacement in cadavers thus treated, and perhaps my smaller percentage is because all the subjects upon which I experimented were males. Upon the relations of these peritoneal folds and their retentive function the important paper by Weisker (160) may be consulted (*vide also* Vol. III. p. 870).

Displacements of the kidney, not attended with any considerable degree of mobility, have been described from time to time; but these malpositions are, for the most part, of anatomical rather than of pathological interest, and seldom cause any marked disturbances of function. In instances described by Hohl and Albers-Schönberg, a pelvic kidney was an obstacle to delivery.

The kidney has normally a certain degree of mobility. Oncometric experiments shew that the healthy organ varies in size with the varying conditions of blood-pressure, and of vascular dilatation and contraction (42). The surrounding organs are liable to corresponding variations; and, in consequence, the exact contour of the kidney, faceted by the pressure of neighbouring parts, is by no means constant. The condition ascertained in the bodies prepared by Professor Cunningham's ingenious

method—in which the antero-external surface is transversely ridged between the hepatic and colic areas—represents a common but by no means an invariable result of this mutual visceral moulding.

Abnormal Mobility.—Almost all possible gradations in mobility have been observed, from the normal fluctuations in size just mentioned, and the normal alterations in position in the different phases of the respiratory cycle¹ and in different postures of body, to the extreme condition of “floating,” in which the organ can be grasped by the fingers through the abdominal wall, and moved upwards and downwards by external pressure. Sir K. Franks (44) recommends the following simple method of testing abnormal mobility. The patient is placed on the back, or else in the latero-prone position, and the surgeon grasps the flank with his left hand, pressing his thumb in front below the costal arch and the fingers behind below the twelfth rib. If the kidney be abnormally movable it can be felt at the beginning of expiration below the grasp of the hand. If the right hand now press on the tumour when the left has relaxed its grasp the gland can be felt to slip upwards into its normal position. This method, however, is not always practicable on account of the conditions of the surrounding viscera. Kuttner regards the deviations of every kidney which can be felt to move with respiration as pathological; but this has been contested by Paul Wagner (*vide* also p. 648).

There are two structural conditions in which the kidney exhibits an abnormal degree of mobility. The rarer of these is that in which the kidney is partially or wholly enveloped in a mesonephric fold of peritoneum: to this form the name Floating Kidney is limited by Jenner and Newman. This anomaly is generally considered, but with insufficient reason, to be congenital: the possibility of the secondary production of a peritoneal fold is too well known to anatomists to exclude the possibility of the mesonephric fold being an acquired condition. Examples have been described by Girard, Roberts, Crum, Howitz, Priestley, Henderson, Franks, Steven, and others. In Dr. J. L. Steven's case there was undoubted evidence of displacement from tight-lacing. In an instance noticed in the dissecting-room, the peritoneum clothed the back of the right kidney and the upper end of the gland, reaching to the lower border of the hilum, but the lower border was not completely enveloped; the ascending colon was displaced nearly to the middle line, and the renal vessels were elongated and tortuous. Cases of this kind cannot be clinically distinguished from those of the second form, and the methods of treatment are practically the same (Bruce Clark). If, however, the existence of a mesonephric fold be suspected, it may be advisable to adopt the anterior intraperitoneal method of fixation.

In the majority of cases there is no mesonephric fold of peritoneum, and the gland moves within a lax areolar capsule. Hilbert distinguishes

¹ Landau denies the movement of the kidney with respiration, but Litten and Israel have proved that such movements actually take place.

two grades of these cases: in the first only the inferior pole and less than the lower half of the kidney can be felt; this he calls the "palpable kidney," and it corresponds to Glénard's first stage: in the second the whole kidney can be felt, and can be isolated with the fingers; this he calls the "movable kidney." Glénard recognises four stages of this grade; his second form is that in which nearly the whole kidney is palpable below the ribs, but the finger cannot be pressed above the upper pole. His third stage is that in which the whole organ can be felt by pressure, and the finger pressed above the upper pole. His fourth stage is that in which the kidney floats independently of the respiratory movements. Sometimes a kidney which remains high, and is not prolapsed, may undergo rotation. Usually the name movable kidney is indiscriminately used for examples of all grades (Jenner), and the condition of mobility has been named nephroptosis.

This condition is met with more commonly in females than in males. From the masses of statistics which have been collected in various countries, it appears that marked pathological mobility exists in about 10 per cent of females and 2 per cent of males. The right kidney shews this condition more commonly than the left, in about the proportion of 8 to 1. This is due partly to the differences in the kidney bed and fascial covering already noticed, and partly to the peculiar relations of the peritoneum on the right side to this region, which make it possible for a right colon loaded with faeces to drag down the right kidney, whereas the left colon, being more firmly fixed, could not displace the left kidney. According to many observers it is as common among the rich as among the poor, and as frequently met with among nulliparae as in those who have borne children.

It is most commonly met with between the ages of thirty and forty; but cases in children have been described by Hirschsprung, Keppler, Steiner, Wilks, Haward, Albarran, Drummond, Gilford, and others.

The character of the mobility is not always the same; the gland may slip up and down within the loose capsule, the motion being compared by Mr. H. Morris to "cinder-shifting" (104); or the kidney and its capsule may move on the hinder wall of the abdomen. In this case the gland may slip beneath the peritoneum, or the serous membrane may be attached to its surface anteriorly; but the marginal connexions may be lax enough to allow of the gland moving forwards and inwards, dragging the membrane with it. Cases of this kind, such as those described by Jago and Gilford, simulate the true floating kidney. Indeed, it is so difficult to draw the line between them, that it is probable that some of the examples which have been referred to that group may really be of this nature.

These conditions are rarely noticed in the dissecting-room, owing to the position in which the body is dissected, and to the increased solidity of the adipose capsule after death. Comparing the records at different places, it would appear that out of 20,000 autopsies this condition has been only recognised once in every 600 bodies examined.

The usual direction of the displacement is downwards, forwards, and inwards; and, in slipping, the organ usually rotates so that the upper end and outer border move forwards, and the hilum is directed inwards and a little backwards; the extent of the motion being apparently limited by the length of the vessels. This rotation forwards of the right kidney has been attributed to the pressure downwards of the liver. Adhesions or alterations in the surrounding viscera may lead to modifications in the direction of the displacement. The records of operations testify to the various positions which the gland may assume. Mosler found the gland with the hilum directed upwards, and its convex border lying horizontally. In a case described by Dr. Goodhart the kidney was completely rotated on its long axis so that its ventral surface was turned backwards. All forms are usually associated with a medial displacement of the ascending colon, and the gland is generally below the level of the duodenum (Aberle). In many cases there is a remarkable absence of perinephric fat, but this is by no means invariable.

Causes.—Nephroptosis is not uncommonly associated with hernia or retroflexion of the uterus, and sometimes it is part of the general relaxation of visceral connexions named enteroptosis, which has been described by Glénard (*vide art. "Visceroptosis," Vol. III. p. 860*). Landau noticed that in most of his cases the abdominal walls were flaccid; but the kidneys are not movable in all cases of pendulous abdomen. Any conditions which relax the abdominal walls certainly seem to dispose to this affection; and in this manner we can explain the mobility of the two kidneys noted by Siredey after hysterectomy. The range of motion varies from 3 or 4 cm. to 25 cm. In a case recorded by Dr. Bindley the kidney is described as moving under the peritoneum over a space which is called a circle with a diameter of 8 or 9 inches.

The disposing causes are relaxation of the abdominal wall, preternatural shallowness of the kidney bed, diminution of the perinephric fat, and congenital elongation of the vessels; possibly a wide interval between the layers of the mesocolon may also be named in this category. In the ancient description of dislocation of the kidney given in Pedemontanus' edition of Mesue's works, too frequent warm bathing is assigned as a disposing cause (1581, p. 74 f.). The immediate cause of the dislocation may be a blow, a fall, a twist of the spine, or the carrying of a weight on the back when the body is bowed forwards, violent coughing, or straining in vomiting or parturition. Sir F. Treves has seen a normal kidney worked out of its place by a vigorous masseuse who mistook it for a faecal mass. Its frequent association with pregnancy may be due to the disturbance in that condition of the peritoneal relations of so many of the viscera. Cruveilhier long ago pointed out the influence of tight-lacing as a cause of displacement; and this cause has been reaffirmed by many later writers; in most cases, the tight-lace line on the liver is on the same level as the upper pole of the kidney, so that pressure on the liver may act through it on the right kidney and may dislocate it. The displacement thus caused is an anteversion of the

upper pole of the kidney, as has been shewn by Wahrmann. Wolkoff and Delitzin shew that the displacing effect of tight-lacing depends on the level of the line of greatest tension ; when that is on the level of the twelfth rib the effect is less liable to cause displacement than when it is on the level of the ninth or tenth rib. On the other hand, Becher and Lennhoff found the palpable condition of the kidney in 6 out of 24 Samoan women who had never worn any constraining garment. The drag of heavy garments fastened round the waist also exercises a displacing influence ; and this drag is even more injurious in the woman than it would be in the man on account of the smaller lumbar curve and the greater shallowness of the bed of the kidney in females. The wearing of high-heeled shoes is also blamed by von Korányi as a disposing influence by altering the lumbar curve.

In many cases, falls, fits of coughing, the jolting of carriage exercise, violent retching, and so forth, have led to the first recognition of the condition, if they have not been its producers.

Symptoms.—Out of 270 cases in which nephroptosis was determined by palpation, there were no symptoms of distress in 130 ; of the remainder, 72 suffered from various neuroses arising from the uneasiness felt in the kidney, from slight pressure effects, and from apprehension that this mal-position might at any time give rise to more serious trouble ; indeed, the majority of patients affected by it are neurotic, and in such the subjective symptoms may not disappear after nephropexy. In 68 of these cases the condition was accompanied by symptoms of a more serious nature (Curschmann). The sensation is one of weight and dragging with occasional colicky pains, and a sickening feeling when the kidney is pressed upon. This pain increases markedly during the incidence of the catamenia. Sometimes these sensations are intermittent, and have been compared by some patients to the sensation of quickening ; indeed the symptoms have actually been mistaken for pregnancy (23, 24). In some cases the symptoms disappear during pregnancy.

The more troublesome effects of nephroptosis are twofold, disturbances of the digestive canal, and obstruction of the ureter or the renal vessels. Besides these there are certain pressure effects, such as "kidney-pain," in the knee, heel, or along the outer side of the thigh, and also along the genito-crural nerve in males, together with neuralgic pains in circumscribed areas of the body-wall ; sometimes on the opposite side to that of the displaced kidney. The pain is said to be more severe in cases of displacement of the left kidney (Suckley). In rare cases oedema of the right leg has been seen from pressure on the common iliac vein (Landau) ; there is at least one case on record of thrombosis of the inferior vena cava (Girard).

The disturbances affecting different parts of the digestive canal are sometimes very severe. Mathieu states that the percentage of cases of movable kidney in dyspeptics is very large ; and it is well in cases of unaccountable disorders of digestion to investigate the condition of the kidney. The symptoms are gastric pain, loss of appetite, frequent

vomiting, and the other signs of gastric catarrh ; the bowels are often obstinately constipated ; sometimes jaundice supervenes, lasting a few days, disappearing and recurring. In some cases the resulting exhaustion has almost proved fatal (Faulder White). In other instances intestinal obstruction has been attributed to renal pressure (Rollet, Dora). The gastric symptoms, first described by Dietl in 1864, are liable to sudden and violent exacerbations, or "gastric crises," attended with abdominal tenderness, and sometimes with a slightly raised temperature. These symptoms last a day or two, disappearing if the patient continue recumbent ; but are apt to return when the body reassumes the upright position. During the crises there is usually a transitory jaundice. In rare cases exacerbations of this nature have ended in peritonitis which has proved fatal (Berry).

The amount of displacement is not necessarily commensurate with the severity of the symptoms. Edebohls has noticed that sometimes the cases with the most distressing symptoms are those in which the kidney has a comparatively small range of movement. This is probably on account of the greater frequency of the displacement in highly neurotic or hysterical persons. Edebohls also noted the frequent concomitance of wandering kidney with disease of the appendix, and he explains this by the pressure which a displaced kidney may exert upon the superior mesenteric vein interfering with the return of the blood from the appendix.

Another series of disturbances may be met with in cases of nephroptosis. After some rapid or violent movement there is a sudden accession of intense and sickening pain ; the abdomen becomes distended ; the region of the kidney becomes excessively tender ; giddiness, faintness, and sometimes delirium supervene ; the pulse is small ; the skin is covered with a cold sweat ; the urine becomes scanty, dark in colour, and sometimes contains albumin and tube-casts. The symptoms increase for three or four days and then subside, recovery being generally accompanied by a copious flow of clear urine. These violent attacks have been attributed by Dietl and Ebstein to the wedging of the kidney into the subperitoneal tissue, and by Gilewski to acute hydronephrosis. To this condition the name renal incarceration has been applied. Landau, however, from his own experiments, as well as from those of Robinson and of Perls and Weissgerber, has suggested that these symptoms are due to torsion of the renal vein, as the pathological conditions are very like those which result from the experimental deligation of that vessel. Dr. Newman also in the course of several operations has verified the existence of this vascular torsion due to rotation of the kidney, giving rise to paroxysmal haematuria (113, 114). In these cases the temporary albuminuria and tube-casts were due to mechanical hyperaemia ; and Dr. Newman found in one case that the rotation of the kidney around its shorter axis had twisted the ureter and blood-vessels round each other.

Another series of distressing symptoms may arise from obstruction of the ureter occurring in a like manner from the rotation which

accompanies the descent of the kidney. The same kind of kinking which has been described as affecting the veins must take place in the ureter ; and this, by its frequent repetition, leads in process of time to dilatation of the pelvis of the kidney, and to hydronephrosis. The mechanism of this dilatation has been described by Landau. Cases illustrative of this effect have been described by Hare, Pernice, Ahlfeld, Cole, Clement Lucas, and Morris (105). In some of the 83 cases described by Terrier and Baudoïn it is shewn that the ureter has become permanently distorted by the occurrence of local inflammatory action producing adhesions. For experiments on the mechanism of these intermitting hydronephroses, see Tuffier (153).

As a consequence of the interference with the vessels due to displacement, the movable kidney is liable to atrophy, this change being secondary to the displacement. In other pathological conditions in which the kidney increases in size and weight, displacement may take place as a secondary consequence of the enlargement. Thus tuberculous, carcinomatous, and sarcomatous kidneys may become movable and slip downwards. Calculi have also been found in displaced kidneys, and consequent pyelitis has been described by Dickinson, Fritz, and Hickinbotham. Whilst in general there is very little change in the nature and amount of the urine in nephroptosis (Rosenstein, Henoch), yet sometimes there is periodic polyuria, as in the case described by Oppenheimer. Apolant accounts for this by supposing the secretory nerves to be stimulated by the displacement.

As a collateral reflex concomitant of movable kidney tachycardia has been noted by Eccles. Certain conditions of the surrounding viscera have been occasionally found to accompany nephroptosis. The liver frequently shews deformation from the same causes as those which have caused the renal displacement, especially from tight-lacing ; and the kidney may be adherent to the anterior edge of its right lobe. The gall-bladder has been found dilated in a few instances (106).

But the most characteristic of these changes in neighbouring organs is dilatation of the stomach, attributed by Bartels to the forward displacement of the gland pressing on the fixed descending portion of the duodenum, and so mechanically obstructing the normal passage of the chyme. This opinion is supported by Mathieu (99), Stiller, and Müller-Warneck. In Sir K. Franks' case a peritoneal band from the upper portion of the kidney was attached to the duodenum in such a manner that, when the kidney was drawn down, the band dragged upon the duodenum and kinked it, thus practically occluding its lumen. Bands closely connecting the ligamentum hepato-duodenale with the peritoneal investment of the front of the kidney are not infrequent in these cases ; displacement of the kidney must of necessity cause some interference with the bile-duct. This is probably the mechanism producing the temporary jaundice accompanying the gastric crises, and the dilatation of the gall-bladder. Edebohl's opinion that the gastric crises are due to traction upon the nerves of the solar plexus is conjectural, and insufficient to account for the gastric enlargement and jaundice. Dr. Newman's suggestion that

the jaundice is the result of concurrent biliary colic or catarrh of the bile-duct leaves the frequency of the coincidence unexplained, as does that of Lindner that the jaundice arises from a reflex spasm of the bile-duct. Adhesion of a movable left kidney to the descending colon has been met with as a result of circumscribed adhesive peritonitis.

Diagnosis.—Generally speaking, the diagnosis of movable kidney is not difficult; careful palpation by Franks' method usually suffices to detect the tumour. The peculiar sickening sensation when it is squeezed, and the position and form of the swelling, are characteristic. Sometimes there is a clearer percussion note than usual in the lumbar region (Guttmann); but this is a very variable character. I have found the usual dull percussion note in a case in which the kidney was much displaced; and Landau has also noted the untrustworthiness of this sign. In very thin persons the pulsation of the renal artery has been felt.

There are no pathognomonic symptoms of movable kidney; but in cases in which unaccountable gastric or renal crises occur a movable kidney may be suspected. As most of the conditions which are liable to be confounded with it shew distinctive characters, in obscure cases, when the tumour itself is not distinctly palpable, the diagnosis is generally arrived at by a process of exclusion. Faecal accumulations, hydro-salpinx, omental tumours, cancer of the colon, enlarged gall-bladder, the "tight-lace lobe" of the liver, ovarian tumours, and hydatid disease have all been taken for nephroptosis, but can usually with care be discriminated. The diagnosis of enlarged gall-bladder from movable kidney is treated more fully in the chapter on "Diseases of the Gall-bladder," p. 245.

Treatment.—The treatment of movable or floating kidney is twofold—palliative and operative. In cases in which there are no symptoms, or merely trivial neuroses, the constraint of a tight jersey, put on before the patient rises from bed, careful attention to the bowels, and the avoidance of violent exercises, such as dancing and running, generally suffice to avert more serious discomfort. If these prove insufficient to fix the kidney, some more direct means of support may be used, such as a well-fitting abdominal belt extending from Poupart's ligament to the seventh rib. Several forms of abdominal stays are in use; the best are those invented by Ernst, Philipp, Klaess, or Landau. The retentive apparatus in all cases should be applied during recumbency, and worn whenever the patient rises from bed. Various forms of truss or pad have also been recommended, but, in general, whenever the kidney is freely movable any retentive apparatus is of very little use. Massage has been recommended by Landau and by Eisenberg; and general treatment, especially ferruginous tonics, strychnine, and local douches or shower-baths often prove of service. For local pains hot fomentations and sedatives may be used. Althaus has recommended the hypodermic injection of antipyrin. The pain which sometimes supervenes in these mild cases from unwonted exercise generally subsides with rest, fomentations, poultices, and belladonna plasters.

When, however, the symptoms are severe, and the retentive apparatus does not relieve them, or is not easily borne, the question of surgical interference must be considered. Much discussion has taken place as to the value of and indications for operation. Each case should be carefully considered, especially with regard to the relation of the symptoms to neurasthenia; thus, a movable kidney may induce neurasthenia, or the condition of the kidney may be an unimportant concomitant of the neurotic state. Some otherwise healthy women are rendered incapable of the activities of ordinary life and are completely relieved by nephropexy, whilst in confirmed neurotic women an operation fails entirely. Two operations have been proposed—Nephrectomy and Nephorrhaphy (Nephropexia of the French authors). The former has been advocated by Keppler, who regards a movable kidney as a continual menace to life; but it is a serious operation, and of the 30 cases recorded between 1870 and 1887, 9 were fatal. The first recorded extirpation of a movable kidney was performed by Gilmore of Mobile, Al., in 1870. Of the fatal cases one is interesting, as the excised gland proved to be the only kidney possessed by the patient, who in consequence died of uraemia on the eleventh day (Polk). This operation is now practically discarded.

The operation of nephorrhaphy—suture of the movable kidney to the abdominal wall—was introduced by Hahn in 1881, but his method has been much modified by later operators. It was first practised in this country by Dr. Newman (112), and is a much safer operation than nephrectomy, the statistics of 1000 operations shewing a mortality of 1·8 per cent. These statistics justify the term “simple and safe,” which Mr. Clement Lucas has applied to the operation.

The different methods of nephorrhaphy have been experimentally investigated by Van der Lee and Triomi. The operation is usually performed by the lumbar incision. The objects of the operation are to replace the kidney in its proper bed—neither too high lest it be pushed down by the liver, nor too low lest it should be painfully pressed upon by the corset,—to fix the kidney and its capsule to the abdominal wall, to attach the kidney to its capsule, and to reduce the size of the cavity in which the kidney moves. The method of fixation need not be here described; its object is attained by simple suture, or by partial decapsulation and the promotion of adhesion of the separated flaps of capsule to the abdominal wall. The best sutures are of kangaroo tendon; they must be strong, as Dr. Newman has found that those which traverse the kidney substance are very rapidly destroyed. Two to four stitches are usually enough, the sutures being inserted as widely apart as possible in the gland (Treves).

In all cases the patient must be kept recumbent for about six weeks after the healing of the wound, abstaining from active exercise for at least three months longer, and should wear an abdominal belt for some time afterwards. The results of the operation as given by different authors shew that 65 per cent were completely successful, 15 per cent were partially successful, and 20 per cent were failures.

When nephroptosis is a part of a general condition of visceroptosis it must be treated accordingly (Treves (148), De Renzi) (see also article "Visceroptosis," Vol. III, p. 881). The treatment of hydronephrosis, when complicated by mobility, differs in little from that occurring when the gland is in its normal site (see article "Hydronephrosis," p. 676).

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A. M.

OTHER DISEASES OF THE KIDNEY

By HENRY MORRIS.

I. ABNORMALITIES OF THE KIDNEY.—It is important from the clinical as well as from the anatomical point of view to realise that the kidneys may be abnormal in Position, or in Form, or in Number.

1. **The Abnormalities of Position, or Misplacements, of the Kidney.**—A misplaced kidney is often somewhat misshapen ; it may also be movable as well as misplaced. Since the movable kidneys are described in a special article ("Nephroptosis," p. 633), only the cases in which the misplacement is permanent, that is in which the kidney is fixed in an abnormal position, are described here. The "simple" misplacements are either congenital or acquired.

The acquired misplacements result from pathological enlargements of neighbouring organs, from pressure by tumours, and from tight-lacing. Enlargements and hydatid cysts of the liver have displaced the right kidney down to or below the brim of the pelvis. In other cases the kidney has been altered in direction by pressure, the whole organ becoming turned so that its long axis is in the antero-posterior direction with the upper end projecting forward between the liver and the colon. Or the kidney may be displaced downwards or laterally, or rotated so that its hilum looks either upwards, outwards, or directly forwards or backwards.

The congenital misplacements which are most common (after the horse-shoe kidney) are those in which the kidney occupies a position over the sacro-iliac synchondrosis, or in front of the promontory of the sacrum or between the rectum and bladder, or by the side of the uterus, or just below the bifurcation of the aorta, or in the false pelvis just above the outer end of Poupart's ligament. The suprarenal is occasionally, though by no means always misplaced along with the kidney ; indeed, it is very rarely so when the misplacement is into the false or true pelvis. In structure the misplaced kidney is, as a rule, normal. It is much more frequent for one kidney to be misplaced than for both, and the left is somewhat more frequently at fault than the right. When the left kidney occupies the corresponding iliac fossa there is generally no sigmoid flexure in the left fossa, but the colon crosses the middle line and the rectum commences on the right side of the sacrum. Malformations of one or other of the genital organs are often associated with misplaced or malformed kidneys.

The acquired, like the congenital misplaced kidney, has often been mistaken for an abdominal tumour. It has also been known to obstruct or otherwise complicate labour, and when in the neighbourhood of the uterus and in contact with the ovary to give rise to severe suffering at

the menstrual period. When occupying a position within the true pelvis the misplaced kidney may be detected accidentally by vaginal or rectal examination, and the diagnosis of the true condition becomes difficult if, as happens both in acquired and congenital instances, the misplaced organ has not the normal outline of the kidney. In these circumstances serious suffering and other grave symptoms have been present, and have led to fatal disasters in practice.

The diagnosis will rest chiefly on the unchanging size, on the texture, form, and elasticity of the misplaced body, and in the want of the normal fulness, resistance, and dull note on percussion in one or the other loin. Pressure on the mass may give rise to the peculiar disagreeable, sickly, faint sensation without actual pain, which is sometimes experienced when pressure or compression of the kidney is made, and which in some persons is as characteristic as when pressure is made on the testicle.

2. The Abnormalities of Form, or Malformations of the Kidney.—The kidney becomes greatly changed in outline and dimensions by various diseases, such as the several kinds of nephrectasis, polycystic and other cystic enlargements, new growths, tuberculosis, and atrophy from nephritis. These are described under their respective headings. Here we are concerned only with congenital malformation of the kidney. Besides varying greatly in size the kidney may be congenitally malformed either with or without fusion with its fellow. The commonest of all the variations from the normal size or shape is the so-called congenital atrophy. In these cases the kidney may be lobulated as well as small, but always possesses an amount of secreting structure weighing from three-quarters of an ounce or less to one ounce and a half, or a little more.

The malformations of a single kidney result in an organ of hour-glass shape, or prismatic, or discoidal, or very deeply lobulated, or trilobate, or almost divided by a deep transverse fissure; also there may be many departures from the normal as regards the situation of the hilum and the relations of the body of the kidney to the ureter and renal vessels.

The malformations from fusion of the two kidneys are very varied; the best known and most frequent by far is the horse-shoe kidney. Fusion is always accompanied by some displacement, the renal mass being generally situated at a lower level and nearer the middle line than the normal position.

3. The Abnormalities of Number.—*A. Cases in which there is only one Renal Mass.*—These are of three varieties: (a) A symmetrical kidney in which there is an entire absence of one kidney, the other being present or normal; (b) Solitary kidney in which there is fusion of the two kidneys; (c) Imperfect or rudimentary development of one kidney in which the only representation of a second kidney is a mere mass of connective tissue, perhaps of the size of a horse-chestnut, a horse-bean, or less, or a cyst or congeries of minute vesicles, with traces of renal tubular tissue at the upper end of the ureter; (d) In the fetus both kidneys have many times been found to be entirely absent. In a large majority of cases in which one

kidney is entirely absent or of the most rudimentary character the ureter is absent also, but when an atrophied kidney is present the whole of the ureter is as a rule present. Where no vestige of emulgent vessels or ureter exists it is certain that no kidney existed either; and even though emulgent vessels and ureter are not wanting, the congenital absence of the kidney may be inferred if nothing in the form of a little mass of connective tissue, cyst, or congeries of vesicles is to be found in the renal region.

Fused kidneys take on many different shapes besides the horse-shoe shape; they are generally situated on one or the other side of the lower lumbar vertebrae or within the area of the true pelvis; there are great irregularities as to their blood-vessels and ureters. They are liable to the same affections as the normally formed organs; thus renal calculi, the several forms of nephrectasis, tuberculosis, and new growths may each affect one part, and one part only, of the united or combined organs. When situated within the pelvis they may give rise to the same symptoms, the same difficulties in diagnosis, and the same errors of treatment as the similarly misplaced single kidney.

B. *Cases in which there are more than Two Kidneys.*—Supernumerary kidneys are very rare, and have been found usually after death, but in one case at least a third kidney was found in the course of an operation (Watson Cheyne).

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II. CLINICAL EXAMINATION OF THE KIDNEY.—In every case of suspected renal disease answers must be obtained to three questions: (1) Is the kidney really affected? (2) Is one only, or are both, affected? (3) If one only, which kidney is at fault?

Inspection.—The front of the abdomen and the loin should be uncovered to the skin. If the kidney is normal in size, in situation, and

in fixity no evidence of its existence is afforded by inspection. If on the other hand it is "floating," or enlarged by calculus, tuberculosis, new growth, or any variety of nephrectasis, it may be readily revealed to the eye of an experienced observer. A floating kidney is often noticed in a thin person lying immediately beneath the anterior parietes. An enlarged kidney may efface the natural hollow of the loin, and if of large size it will even bulge the abdominal wall laterally or in front.

Palpation.—The patient should lie on his back with the shoulders slightly raised on a firm pillow, and the spine at rest, not arched as patients are so apt to make it as soon as the examiner attempts to pass his hand behind the patient's loin. The lower limbs may be lying straight, or with the knees a little bent, and the patient should breathe naturally. The examiner then places the fingers of one hand on the loin and the last rib, the fingers of the other hand in front just below the thoracic margin. He should be on the same side of the patient as the kidney he is examining, and should kneel or sit so as to have the lowermost forearm just above the level of the mattress. With the fingers behind, the loin should be gently but firmly pressed forward and so sustained; the fingers in front should gently but firmly depress the abdominal parietes upwards, backwards, and outwards immediately below the margin of the corresponding side of the chest. The kidney if enlarged or displaced will now be felt between the two hands; and even if not enlarged the lower third or half of the organ will in some persons be detected during natural respiration. The patient should next be directed to take a long deep inspiration, and then suddenly, but without muscular effort let his chest recoil; in other words, he should make a long-drawn sigh. The hand behind still maintains forward pressure on the loin, and the hand in front quickly follows the receding abdominal wall as it becomes relaxed and sinks in the expiratory recoil. By this method the kidney may be seized between the fingers of the two hands before it can regain the position it occupies in quiet respiration. This method is made more effectual if the patient takes a second or third similar sigh while the examiner maintains throughout, and increases after the first and second sigh the deep pressure before and behind. By alternately pressing harder with the fingers, first of one hand and then of the other, while the other fingers are kept still, the movement known as "ballottement" is obtained.

Percussion is only of importance in diagnosing enlargements of the kidney from enlargements of other organs or tumours unconnected with the kidney (see section "Diagnosis of Renal from other Tumours," p. 725).

The *x*-Rays have now been brought to a pitch of accuracy—so far as the results they yield in the hands of experts—that calculi can be diagnosed with the greatest accuracy if care be taken to repeat the exposure of the patient to the rays in all cases in which uncertain or doubtful shadows are shewn and require to be checked (*vide* Vol. I. p. 481).

The Phonendoscope, except in the hands of its inventor (Bianchi), has not yielded helpful results.

The Freezing Test or Cryoscopy (*vide* p. 535).

The Phloridzin Test consists in the production of artificial glycosuria by the administration of phloridzin. Normally sugar appears in the urine within half-an-hour after the subcutaneous injection of the drug. If the functional activity of the kidneys (or of the only kidney with a patent ureter) is impaired, the appearance of the sugar in the urine is delayed.

The Colour Tests.—Many substances have been used to test the permeability or excretory capacity of the kidneys, but most of them require a very careful, and some a very prolonged analysis of the urine. Methylene blue and indigo-carmine are, however, free from this disadvantage. The results are obvious to the eye. The method of applying these colour tests is as follows :—

(1) Empty the bladder of the patient ; (2) Inject a sterilised solution of the colouring-agent into the buttock or thigh ; (3) Get the patient to pass water soon after the injection and every half-hour or hour subsequently for some hours.

In the case of methylene blue 1 c.c. of a 5 per cent solution ought to cause the blue to appear markedly in the urine within an hour, and it should increase for several hours.

In using indigo-carmine 20 c.c. of a 0·4 per cent of the dye are injected, and in less than a quarter of an hour the dye appears in the urine, if the functional power of the organ or organs is good ; the longer its appearance is delayed the less good the excreting power of the kidneys or kidney.

Segregators or Separators, and the Ureterocystoscopes.—Happily it is only in a very small proportion of cases in which the organ specially affected (when both are not) cannot be ascertained by various symptoms, and the methods of clinical examination just described. In those in which it cannot be so determined resort may be had to methods by means of the instruments now named. After many years of experiments and trials and modifications these methods still remain uncertain and unsatisfactory. The instruments ought certainly to be employed only by the few specially practised in their use, not by the general physician or practitioner. Even in the hands of the most acknowledged experts they have led to errors of diagnosis and treatment which would be deemed ludicrous if they were not so serious. They are too fraught with many risks and dangers. But it would be quite out of place to describe the technique of the methods themselves, and of the precautions with which their employment ought to be safeguarded, in a work on "Medicine." The reader must refer to treatises on Renal Surgery for further details.

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III. ANEURYSMS OF THE RENAL ARTERY or its branches are amongst the rarest of all aneurysms. They are either traumatic or spontaneous, either false or true.

True Aneurysms are those the walls of which are formed of some or all of the arterial coats. They are commonly small, being usually no larger than a haricot-bean or a hazel-nut, although in one case a sacciform aneurysm attained the size of an apple. They occur as the result of injury, and when spontaneous as the result of degeneration of the coats of the vessel from disease, or in association with infective endocarditis. They have been met with about equally in males and females, and generally in persons over forty years of age. Mr. Barnard, however, has reported two cases of spontaneous aneurysm in children—one in a boy aged nine years, a cured and calcified aneurysm of the right renal artery; and one in a little girl in whom an aneurysm which ruptured was associated with infective endocarditis. As long as it remains unruptured a sacciform aneurysm gives rise to no symptoms, and produces no distinct changes in the kidney or neighbouring parts; although when situated within the renal capsule the little tumour may press aside and more or less flatten some of the renal tubules but without actually destroying them, or may even assist in causing a certain amount of atrophy of the kidney. Rupture of a sacciform aneurysm into the renal pelvis has proved fatal from profuse haemorrhage—the blood and blood-clot passing into the bladder has flowed away through the urethra.

False Aneurysm occurs (a) from the giving way of a true aneurysm; or (b) from the yielding of a thrombus which temporarily closed a ruptured artery; or (c) by the immediate outpouring of blood from a ruptured artery. Its walls are formed by the renal parenchyma, or the fibrous capsule of the kidney, or the renal pelvis, or, if the blood extends beyond the limits of the kidney, by the matting together of the surrounding tissues or neighbouring organs. The aneurysm may be completely outside the kidney and completely or partially envelop it. Traumatic aneurysms of the renal artery and its branches occur much more frequently in males than in females, and in the active periods of life.

A false aneurysm may go on slowly increasing for several years. It gives rise to a tumour of great clinical importance, sometimes of large size, puzzling to diagnose, dangerous to treat, and hitherto invariably fatal if not operated upon.

Etiology.—Of 26 cases which I collected and analysed, 14 were traumatic, 10 spontaneous, and 2 unclassed. Of the 14 traumatic cases, 3 were sacciform when found after death, 10 were false, and 1 doubtful. Of 12 false aneurysms, 5 were the immediate result of a ruptured vessel, 4 of the rupture of a sacciform aneurysm, 1 of the rupture of a tubular

aneurysm of the trunk of the renal artery, and 1 of the yielding after a time of a thrombus in a ruptured vessel; in 1 the nature was undetermined.

Pathological Consequences.—When a false aneurysm is formed—whether as the direct result of injury, or less directly by the giving way of a traumatic or spontaneous sacciform aneurysm, or the yielding of a thrombus, matters not—serious damage is wrought upon the kidney, and displacement and pressure changes are caused to surrounding parts and organs. Absorption of the parenchyma and distension of the calyces are the result of a very large haematonephrosis; or the blood may be effused beneath the renal capsule between it and the parenchyma, which itself may either be little damaged or become entirely disintegrated; or the blood may be extravasated partly within the renal capsule and partly into the perinephric tissue; or it may be entirely outside the renal capsule. When the blood is partly within and partly outside the renal capsule the kidney tissue may become completely or partially absorbed, or may be spread out in the wall of the false sac as it was in a case of my own in which the kidney had almost completely and the adrenal had completely disappeared.

Symptoms.—Tumour and haematuria are sooner or later the ordinary symptoms of a false aneurysm no matter how formed, whether directly from injury or later by the giving way of a sacciform aneurysm.

Tumour.—A swelling was found in 17 out of 22 cases. It was fixed and not movable on inspiration, nor, as a rule, by bi-manual pressure. The size varied from that of a double fist to that of a tumour filling half the abdomen, reaching from iliac fossa to the dome of the diaphragm, forcing the loin backwards and outwards, and the abdominal parietes forward. The date of the first appearance and the rate of the growth of the swelling vary according to the degree of resistance of the tissues and the firmness of the coagulum which for a time closes the rent in the vessel or (in cases of rupture of a sacciform aneurysm) in the aneurysmal sac. In some cases the tumour was never noticed till some years after the injury. In one case the tumour was only detected a few hours before death, and that on the tenth day after the injury. In other cases the swelling has followed an injury at once, or within a few days.

Pain and tenderness are not marked features, as a rule, though in a few instances pain has been intense.

Pulsation.—This symptom, so characteristic of most other aneurysms, is remarkable by its absence in most of the recorded cases. In one it was present and led to a correct diagnosis; in only 2 other cases out of 21 was it even suspected, and in neither of them could it be positively made out just before or during the operation. Auscultation affords no assistance.

Haematuria is very common and the next most important sign to tumour. Indeed it may be the most important sign, and may possibly be fatal before any tumour forms. It is most frequently the earliest symptom, and may precede a tumour by many months or even a year or

two. In traumatic cases the period after the injury at which it first occurs is very variable, and even when commencing immediately after the injury it may cease after a day or two, and then recur, in an intermittent manner, after some months; or, on the other hand, it may be continuous for months and even up to the end of life.

General symptoms are such as would be expected from loss of blood and from the pressure effects of the tumour.

Diagnosis.—No symptoms are known to be caused by a small sacciform aneurysm, hence the question of diagnosis does not arise. It is possible that a small aneurysm of a branch of a renal artery within the hilum or calyx may simulate a renal calculus, just as a small mass of tubercle, a cyst, or abscess has at times done. The tumour of a false aneurysm has been mistaken for a renal or adrenal new growth, or for false hydro- or haemato-nephrosis due to ruptured kidney or a ruptured vein; for hydronephrosis, and in Fulton's case for extra-uterine pregnancy. The swelling following rupture or laceration of the kidney is generally developed very rapidly; is attended with great pain, with more or less shock, and if the renal pelvis is lacerated, with a diminution in the quantity of urine passed; later on the urine will probably contain pus. Suppuration with rigors, and high temperature will almost certainly supervene if the patient survive for many days. It must be borne in mind, however, that perinephric extravasations are sometimes delayed for weeks after an accident.

A simple haematoma, or nephrectasis containing blood (*i.e.* a true haematonephrosis) due to a ruptured artery, is indistinguishable from a haematoma or blood nephrectasis due to a ruptured vein or ruptured renal parenchyma.

A malignant new growth of the kidney may pulsate; hydronephrosis is more elastic, less heavy, may fluctuate or only intermit, and is seldom if ever attended by haematuria.

Prognosis.—This is most unfavourable in false aneurysm; all the cases hitherto reported which have not been treated by operation have ended fatally. Four out of five of those which have been operated upon have recovered. A small sacciform aneurysm unless it ruptures does not interfere with life, and hitherto has only been detected at autopsies. The causes of death in the other cases have been haemorrhage from rupture into the renal pelvis; haemorrhage into the peritoneal cavity; extravasation of blood behind the peritoneum; peritonitis.

Treatment.—The only prospect of saving the life of a patient who has a false aneurysm is by nephrectomy and the removal of the whole or the greater part of the aneurysmal contents, after first securing the renal vessels by the transperitoneal route. It would be out of place in this work to give the details of the operation, but no surgeon should undertake the operation without first making himself acquainted with the extreme difficulties and the terrible risks which surround it, and which the experience of the few surgeons who have operated in these cases has shewn it invariably to possess.

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IV. PERINEPHRIC EXTRAVASATIONS.—Air is occasionally found in considerable quantity around the kidney after injury to this organ. The source of the air cannot always be found. In one case it appeared to have gained admission through a perineal incision made on account of a rupture of the urethra, which complicated a fracture of the pelvis. Wounds of the loin, groin, and perineum, whether complicated by wounds of the bowel or not, and fractures of the lower ribs with injury to the lung, may be the causes of this form of extravasation. Retroperitoneal abscess opening into the bowel may give rise to it.

Blood may be effused around the kidney from ruptured artery, vein, or capillaries as a result of violence. The clots so formed may ultimately break down and lead to suppuration. Fractures of the pelvis or lumbar vertebrae, rupture of a muscle, and the bursting of an aneurysm of the abdominal aorta, or of the renal artery, have been causes of considerable circumrenal haemorrhage. The kidney may be pushed forward so completely by the extravasated blood as to present a prominence anteriorly in the hypochondrium.

The symptoms vary with the cause and extent of the extravasation. When the blood is confined to the cellular tissue of one loin, it produces a tumour, sometimes difficult to diagnose from a distended kidney. If the source of the bleeding be a superficial laceration of the kidney, or a rupture of a branch of a lumbar artery, some weeks may elapse before the effusion is sufficient to give rise to any swelling or increased dulness in the loin, and no sign of faintness is noticed at any time; then, after some time longer, the effused blood becomes more solid, the tumour more irregular, and by degrees, perhaps, it is absorbed. On the other hand, the blood-clot may disintegrate; in these circumstances the symptoms of suppuration will arise.

Recovery may take place after very extensive traumatic haemorrhage; but retroperitoneal haemorrhages due to ruptured aneurysm are almost certainly fatal, though, it may be, but tardily so.

If the haemorrhage increase, or suppuration occur, and surgical aid is not afforded, death may follow from peritonitis, due to tension upon the peritoneum or rupture of it; or the colon may be penetrated and

faeces and flatus enter the blood tumour and give rise to decomposition, septic absorption, and death.

When haemorrhage is due to aneurysm, little or nothing in the way of treatment will avail, except an operation and the ligation of the vessel on which the aneurysm is situated in the case of the renal artery or one of its branches. When due to injury, the treatment must be based upon the principles stated in dealing with injuries to the kidney (H. Morris).

Urine is extravasated into the loin behind the peritoneum from a rupture of the kidney involving the calyces or renal pelvis, from direct penetrating wound the result of operation or accident, or as a consequence of ulceration of these parts. Ulceration of the ureter, due to injury or the pressure of a calculus within or of a tumour on the outside of the duct, may cause urinary extravasation into the loin or iliac region. The inflammation of the cellular tissue, resulting from urinary infiltration, may run on to suppuration, giving rise to a lumbar or inguinal abscess. Healthy urine alone is but little irritating; it is the mixture of blood and urine which tends to decomposition and suppuration. If the quantity of urine effused be small, the cellulitis, stopping short of suppuration, may become chronic, spread towards the iliac fossa, and cause contraction of the ilio-psoas muscle. In some instances the effused urine becomes encapsulated within a thick-walled cyst of inflammatory origin, with the cavity of which the kidney communicates at the point of rupture or ulceration. Sometimes phosphates accumulate in the space occupied by the effused fluid to such an extent as to form deposits which block the drainage-tubes used in treatment by lumbar incision.

The extravasation of *pus* into the perinephric tissue is referred to under Perinephric Abscess (*vide p. 655*).

Faecal extravasation requires no special remark in an article on the kidney.

Treatment.—When the diagnosis is uncertain, but from the fulness and dulness of the loin there is reason to think urine is escaping behind the peritoneum, lumbar incision and drainage are needed. Suppuration must be dealt with by early free incision. If the kidney be greatly damaged, nephrectomy will be requisite.

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V. PERINEPHRITIS AND PERINEPHRIC ABSCESS.—**Perinephritis** is inflammation of the cellular and adipose tissues surrounding the kidney. It may occur at any age, having been met with in quite young children; it appears in three forms—the sclerosing, the fibro-fatty, and the phlegmonous.

The sclerosing variety results in the formation of a thick white firm

fibrous capsule, which occupies the site of the circumrenal fat and may also extend into the neighbouring parietes in the lumbar region, even to the skin. This sclerosis of the adipose tissue round the kidney leads to compression of the vessels and subsequent atrophy ; the organ having been removed in some cases without there being any necessity to ligature the contracted vessels.

The fibro-fatty variety consists in the over-development of the normal envelope of the kidney associated with a certain amount of induration, so that the organ may be concealed in large masses of fat and fibrous tissue which may even penetrate into its substance, rendering its recognition extremely difficult.

The phlegmonous form, which constitutes perinephric abscess, includes all kinds of pus-formation in these tissues. It is rare before puberty.

Etiology.—Perinephritis is most commonly secondary to a suppurative lesion of the kidney. It may, however, arise primarily in the cellular tissue ; or be secondary to suppuration in some neighbouring organ ; or be propagated from some distant one, such as the ovary, Fallopian tube, broad ligament, uterus, or caecum. Perinephritis occurs more often in men than women : it complicates the specific fevers, infective diseases, and puerperal sepsis. It occurs also after exposure to cold, and in some cases after operations on the lower genito-urinary organs, independently of any affection of the kidney. Among local causes are contusions, strains, and wounds, including infection from an unclosed ureter after nephrectomy for pyonephrosis. The greater number of instances, however, are secondary to disease in the kidney.

Arising by infection from neighbouring organs, circumrenal abscess may be secondary to biliary or intestinal calculus, perforation of the colon, pneumonia, empyema, or pulmonary abscess ; the infecting virus being conveyed by the veins or lymphatics.

Perinephric Abscesses are : (i.) *Primary* extrarenal abscesses, or those which are independent of any fistulous opening into, or other disease of the kidney. These may depend upon injuries, chills, etc., or may follow the acute exanthems ; or the abscess may have extended from a distant part, as the spine, pelvis.

(ii.) *Consecutive* extrarenal abscesses ; in which inflammation of the kidney has spread to the cellulo-adipose tissue (a) by contiguity, but without urinary infiltration ; or (b) as a result of a renal fistula communicating with the surrounding cellulo-adipose tissue. This form is usually due to suppurative pyelitis ; or to tuberculosis, cancer, hydatid or other form of cystic disease ; or to calculus of the kidney.

(iii.) Consecutive to disease of an organ other than the kidney, as of the lung, ileum, appendix, colon, testis, liver, gall-bladder, or one of the pelvic organs.

The pus is situated usually behind the kidney or at one or other extremity of it. In the latter varieties it lies between the kidney and the diaphragm ; or between the kidney and the colon, with a tendency to extend towards the iliac fossa. In most instances extension takes place

so that all these sites are occupied at once, and the limiting wall is made up of the neighbouring viscera agglutinated together and protected by false membranes, whilst the enclosed area is broken up into distinct suppurating foci. The contents may be thick creamy pus or a thin serous or glairy fluid, often with a feculent odour; and in the midst may lie the immediate cause of the abscess in the form of calculi, hydatids, or intestinal matters. The kidney may be free from disease or may contain suppurating points, not necessarily in direct communication with the abscess, but often situated immediately beneath the capsule, and sometimes constituting the proximate cause of the abscess. Suppuration may extend to the liver, spleen, or pancreas, and the intestine may be closely adherent; but the peritoneum is rarely involved beyond being adherent and thickened. In one case, recorded by Dr. Coupland, the pleura and lung were invaded and the pus was discharged through a bronchus. In others, pyothorax has resulted. Below, the abscess has extended to the pelvis and found vent through one of the various natural openings or into one of the pelvic viscera, or has tunnelled along the psoas muscle. Posteriorly it may open superficially in the loin through the triangle of Petit.

Symptoms.—These vary with the cause and acuteness of the disease. When the inflammation is secondary to some distant disease, such as pelvic cellulitis, the symptoms of the primary affection may disguise those of the perinephritis. Extensive sclerosis gives a firmness and immobility to the circumrenal tumour which, taken in conjunction with its position and relations, are quite characteristic.

The constitutional indications of pus in the circumrenal connective tissue are the same as those excited by deep-seated suppuration elsewhere. The febrile temperature in some cases runs continuously high; in others it is intermittent and suggestive of malaria or pyaemia. Obstinate constipation is almost invariable. The urine may be quite normal if the cause of the disease is not in the kidney itself.

Of the local symptoms, those due to pressure are more marked in perinephric abscess than in perinephritis. Pain, deep-seated and often paroxysmal, ushers in the disease; sometimes dull and aching, at other times darting, it courses along the distribution of the lumbar plexus. The pain is greatly intensified by bi-manual compression of the loins.

The affected side will impart a sense of increased resistance and weight long before pus has formed or the abscess is large enough to alter the contour of the part in any way. The skin in the loin is often waxy and oedematous. Fluctuation is frequently very remote, owing to the thickness of the parietes; and in one case, in which six pints of pus were pent up, no fluctuation could be detected on account of the great thickness of the subcutaneous fat. Oedema of the foot and ankle has preceded for many weeks every other sign of perinephric abscess. A peculiar lameness, due to the flexed position in which the thigh of the affected side is retained in order to relieve tension, is often an early symptom. There is usually also disturbance of the digestive organs manifested

by anorexia with nausea and vomiting, and either diarrhoea or constipation.

In perinephritis before suppuration has occurred the spinal column is preternaturally stiff, and the body in walking is inclined to the affected side; stooping is difficult; in the recumbent posture the patient will not extend the corresponding thigh beyond 160° , or in severe cases 130° ; and there is sometimes pain in the knee. These conditions together cause the case to resemble the second stage of hip disease, especially when the thigh is rotated outwards, so that the heel of the affected side during standing rests on the dorsum of the opposite foot. In simple perinephritis there is no tumefaction to be felt in the loin, as in perinephric abscess. Sometimes the symptoms of pleurisy or pneumonia on the affected side are simulated and the patient appears to be suffering from disease within the thorax only. Perinephritis and perirenal abscess about the upper pole of the kidney may be complicated by pleuritic friction, pleural effusion, empyema, expectoration of pus, and dyspnoea. The characters of the pus vary, being in some cases odourless, in others very fetid.

Prognosis.—In a few cases perinephritis ends in resolution before the suppurating stage has been reached. When suppuration occurs, the prognosis depends chiefly on two things, the early and free evacuation of the pus, and the cause of the disease.

When the abscess is primary, that is, not dependent upon renal or other visceral or spinal disease, an opening into it is soon followed by convalescence. If the abscess burst into the peritoneum, rapidly fatal peritonitis ensues.

The persistence of sinuses and the establishment of lardaceous disease usually lead ultimately to a fatal result.

Diagnosis.—The affections which may be mistaken for perinephritis or perinephritic abscess are lumbago, various organic diseases of the kidney, spinal caries, splenic tumours, faecal accumulations in the colon, morbus coxae, psoas abscess, and empyema and abscess of the lung.

The high situation of the pain; the tenderness in the loin; the fact that passive flexion is painless in itself; the free, painless mobility of the hip-joint; the absence of tenderness and fulness over the upper end of the femur; the absence of pain on percussion of the thigh, and the slighter rigidity of the adductors and rotators, serve to distinguish perinephritis from hip disease.

The symptoms of perinephritis are very closely allied in many points to those which accompany appendicitis; but the characteristic feature of perinephritis is that the pain, tenderness, and swelling are first observed and most pronounced in the ileo-costal interspace behind; whereas in appendicitis they are most frequently in the iliac fossa and in front.

Treatment.—Primary perinephritis may sometimes be checked in its early stages by local blood-letting, by means of leeches or the cupping-glass, by hot baths, and hot emollient fomentations or stupes.

When the acuteness of the symptoms has passed, or the inflammation

is of the subacute or chronic character, disappearance of the inflammatory products may follow blistering, or hot fomentations applied over some absorbent ointment such as iodide of potassium or iodide of lead. The bowels should be well opened at the onset by a brisk purgative, and kept acting moderately by enemas or mild laxatives.

Pain must be relieved by morphine given in suppository or by the mouth. The diet should be milk, beef-tea, or something equally simple and as readily digested.

As soon as pus is suspected, it should be searched for at once by an exploratory incision in the loin; and when found must be evacuated through a free incision in this region. There should be no waiting for fluctuation; the increasing fulness, hardness, and tenderness, and perhaps the commencing redness and oedema of the skin, are ample signs to warrant an incision, and even to demand it. Rousseau, among others, pointed out the difficulty of detecting fluctuation, which, he says, is almost always deep, requiring great experience to make out; but the doughy feel of the lumbar region, the increase of the fever and other general symptoms, and perhaps the oedema of the skin in the loin, are indications for a free incision which the surgeon must not hesitate to act upon with promptitude. The incision may be vertical, oblique, or transverse; and after dividing the integument and muscles with the knife, the suppurating area should be entered by the finger. The abscess cavity and kidney should be examined with the finger for a stone; should a renal fistula exist, it must be laid open, especially if the preceding symptoms indicate calculous pyelitis. Any loose sloughs of cellular tissue should be removed by the finger or dressing-forceps. The abscess should be washed out with a solution of iodine or carbolic acid, and a drainage-tube should be inserted. The loin should then be enveloped in a large hot fomentation of cotton-wool soaked in equal quantities of water and carbolic acid solution (1-40); or, if there is redness or oedema, equal parts of lead lotion and carbolic acid solution (1-40). Absolute rest in bed should be enforced throughout convalescence.

Consecutive abscesses, and also some of the less acute forms of primary abscess which do not soften down very quickly, must not be allowed to close too early. On the contrary, the drainage-tubes should be retained until, by the granulating process in the wound, they are forced out by degrees. If in these cases the wound is allowed to close too early, inflammation recurs and pus is formed afresh, which will need a second incision to prevent burrowing far and wide. When a fistulous opening remains, astringent or iodine solutions may be injected, or the granulations should be freely scraped away. If these means fail the callous wall of the fistula should be completely excised and the raw surfaces brought together with the view of their uniting by first intention; but a fistula may persist in spite of the most persevering measures employed to close it. A lumbar hernia may follow the incision for the evacuation of an abscess, or for the examination of the kidney, but excessively rarely does so.

While suppuration continues, nutritious food, tonics, and possibly a regulated allowance of stimulants should be given. The record of cases in which early and free evacuation of pus has been accomplished is very favourable, nearly all ending in recovery. On the other hand, peri-nephric abscess left to itself almost always ends fatally; except in the rare instances in which the matter finds vent by the bowel, bladder, or bronchi, or opens externally.

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VI. TRAUMATIC NEPHRITIS.—Causes.—Wound or contusion of the substance of the kidney, violent muscular strain, the contusions caused by the presence of a calculus. When blood has been extravasated into the cavity of the kidney, and the urine retained there in consequence of impaction of a blood-clot in the ureter, pyelitis and pyelonephritis may arise.

Symptoms.—Rigor; fever; pain. The pain is not constant and may be variable in character, degree, and surface area. Nearly all movements aggravate the pain. If the disease sets in soon after an injury, the urine always contains a trace of blood. Subsequently, in a few cases, pus may be found in the urine. There is a disposition to the formation of gravel and calculus—and, as a consequence, to renal colic—after wounds or concussions of the kidney.

Traumatic nephritis is not usually serious, provided the damage inflicted on the kidney be not great and the large vessels be not ruptured. If severe, the kidney may be softened into a mere pulp.

Treatment.—If the pelvis of the kidney has been penetrated, urine will drain away by the external wound. If the organ has been opened by subparietal laceration or rupture, the chief danger when the large vessels are uninjured is from infiltration of urine mixed with blood into the cellular tissue. Then it may be necessary to lay open the loin by a free incision down to the injured kidney, so as to provide for the free drainage of the extravasated urine and inflammatory products.

When there is no extravasation, small quantities of fluid diet, the application of cold or leeches, relief of the bowel by one good purge or an enema, and opium to relieve pain constitute the usual necessary details of treatment.

VII. SUPPURATIVE NEPHRITIS, PYELITIS, AND PYELONEPHRITIS.—One of the most frequent of the secondary affections of the kidney (secondary, that is, to obstruction to the outflow of urine, to reflex irritation, or to decomposition of urine in the bladder) is suppuration in the pelvis or in the substance of the kidney, or in both.

In by far the greater number of such cases chronic dilatation of the pelvis and calyces precedes suppuration of these parts; and, later, numerous small scattered abscesses occur throughout the renal substance.

It is to this general affection of the pelvis and substance of the kidney from obstruction in the lower urinary passages, or disease of them, that the name suppurative pyelonephritis has been given. It is to this condition that the name surgical kidney has also, but very inaptly, been applied.

Suppurative nephritis, or, in other words, "acute interstitial nephritis, with scattered points of suppuration," occasionally occurs alone, without any affection of the ureter and pelvis of the kidney; this, however, is not commonly the case. Usually acute pyelitis and suppurative nephritis exist simultaneously; but if suppurative nephritis happen to be uncomplicated with pyelitis, the nephritis is prone to be overlooked, because then the urine contained in the pelvis of the kidney, and drawn off by a catheter immediately after washing out the bladder, is acid and without the odour of decomposition. Nevertheless the temperature and other constitutional symptoms ought to correct the fallacy.

Etiology.—Infective lesions of the kidney may arise from the upward extension of inflammatory affections of the lower urinary apparatus, which are by far the most frequent cause of them. In other cases the infection is conveyed to the kidney directly by the blood-vessels, and thence descends along the ureter to the bladder: these are much less common.

A more important distinction consists in the presence or absence of distension of the renal pelvis. Pyelonephritis without distension admits of medicinal treatment, and shews itself by high temperature and other symptoms; pyelonephritis with distension manifests itself by definite physical signs also, and, generally speaking, needs surgical methods.

In the causation of suppurative disease of the kidney the influence of sex is prominent; the very much greater number of cases occurring in men being consequent upon the greater frequency of diseases of the bladder in them; whereas in women similar changes occurring in the kidney are usually associated with morbid conditions of the utero-ovarian system. Arteriosclerosis, associated with interstitial nephritis and enlargement of the prostate, is a frequent disposing cause of bacterial infection of the kidneys in men. In women such infection results from intrapelvic com-

pression of the ureters due to fibromyoma, cancer, peritonitis, adhesive ovaritis, affections of the Fallopian tube, or prolapse of the uterus.

Renal congestion, due to reflex changes in connexion with cutaneous impressions, over-distension of the bladder and particularly to the vaso-motor paralysis accompanying injury to the spinal cord, is an important disposing cause, to which may perhaps be added the influence of albuminuria and defective nutrition of the tissues.

Among exciting causes may be mentioned pyaemia and puerperal infection (which more often induce abscess of the kidney than pyelonephritis), and the allied blood conditions which accompany erysipelas, burns, and osteomyelitis. Of the more immediate local causes are injuries to the kidney or ureter, pelvic cellulitis, cystitis due to septic catheterisation, and frequent over-distension of the bladder from various causes.

Inflammation of the renal substance and pelvis is excited by certain drugs, such as cantharides, copaiba, turpentine, and other diuretic irritants. Robin describes turpentine and copaiba as causes of a catarrhal inflammation, and large doses of cantharides as giving rise to a fibrinous variety. It is doubtful whether these drugs are ever the direct cause of suppuration, but they produce a condition favourable to infection.

Pathology.—The ascent of micro-organisms to the kidney is assisted by the failure of peristaltic contraction and the dilatation which are associated with retention of urine; and again by the contractions of the bladder which are provoked by the obstruction to the natural escape of its contents. Congestion renders the kidney more vulnerable to the entry of micro-organisms, many varieties of which infest the urinary organs, the most frequent being the *Bacillus coli*. These organisms develop more readily in an albuminous fluid, and the arrangement of the blood and lymphatic vessels of the kidney and ureter affords a direct means of invasion in cases of urethritis. Ureteritis leads sometimes to thickening and sometimes to dilatation of the tube, and in a few cases to a sclerosis of the vesical extremity with impairment of the valve-action there. The pelvis of the kidney is subject to similar pathological changes, the walls being either thickened and contracted or thinned and dilated. In acute inflammation the mucous lining is vascular and swollen, covered with glairy mucopus or false membrane, a deposit of phosphates often being added.

Without being distended the kidney may be enlarged, soft, oedematous, greyish in colour, and shewing no distinction between cortex and medulla. The parenchyma may contain cysts, collections of fat, and (in the acute cases) miliary abscesses, or areas of necrosis.

With distension of the pelvis and calyces, the kidney may attain the size of the human head. It may be adherent to the neighbouring organs, tissues, and vessels. The fatty envelope is usually sclerosed and adherent, as is also the capsule. A quart or more of pus may be contained in the renal cavity and all appearance of the gland substance may be lost, nothing of the organ remaining but a fibrous capsule with septa. The lining membrane is often ulcerated or gangrenous. In other cases many

separate abscesses of the renal substance may be present, or the renal cavity may be occupied by primary or secondary calculi.

Microscopically the substance of the kidney may display disseminated cortical or radiating medullary abscesses, with granular and fatty changes in the convoluted tubes, and proliferation of the epithelium of the glomeruli, accompanied by general hyperaemia and the presence of haemorrhages ; in chronic cases sclerosis and suppuration may be found.

Symptoms.—Loss of appetite, furred tongue, disturbed digestion, emaciation, and loss of strength are common symptoms. The skin becomes dry, pale, or jaundiced. There is more or less fever. The symptoms, however, exhibit wide variations, and in some cases are so slightly marked that they attract no notice.

The acute form is ushered in by fever and rigors often accompanied by delirium ; emaciation with severe disturbance of the digestive functions and sweating ensue. The disease may prove fatal by hyperpyrexia or exhaustion in this stage, but more often lapses into the chronic form. This, however, may be established without the initial acute phase. The prominent symptoms then refer to the digestive system, so that most of the patients are regarded as dyspeptics ; and this mistake is the more likely, as the temperature is but little raised. The mouth and pharynx are dry, owing to deficiency of saliva, speech and deglutition are thereby interfered with, and the patient will swallow nothing but liquid. There are vomiting, flatulence, tympanites and commonly constipation, though this last may give place in the later stages to fetid diarrhoea. The patient suffers much from cold, from great depression, and muscular weakness. Walking becomes difficult, and the inability may amount almost to paraplegia. Sleep is disturbed, and there may be nocturnal delirium. The skin is dry, cold, and rough, with detached epidermal scales ; it is often irritable and affected with various eruptions. The circulatory system is commonly not affected, until in the latest stages of the affection the heart becomes weak and irregular. In cases of a mild form the symptoms are little marked, and the patient may be able from time to time to resume his occupation. Nevertheless, progressive loss of flesh and strength and congestion of the internal organs, especially of the lungs, occur, and the patient is liable under the influence of chills or fatigue to manifest the more acute symptoms, or to relapse ultimately into the more severe chronic condition mentioned above, dying of urinary cachexia without actually presenting the definite symptoms of uraemia.

Locally the signs vary according as there is pyelonephritis with or without distension, and according as this is permanent or intermittent. There is pain in the region of the kidney, and tenderness on deep palpation, or pain elicited by movement when calculus is present. Pyelonephritis without distension occurs mostly in old people, often in the course of chronic cystitis, and directly on exposure to chill or catheterism. The onset is marked by fever, or may supervene gradually with pain in the lumbar region and polyuria, accompanied by albumin and casts. The daily secretion of urine is increased to from four to eight pints. It is

pale and of low specific gravity, and presents a greyish-white deposit of pus with a supernatant cloud of mucus or liquor puris on standing. On expulsion, the urine is uniformly opalescent or may be slightly denser towards the end of micturition; early in the disease it is acid, but later it becomes neutral or alkaline. The urea is diminished, albumin is present independently of the pus, and the tendency to putrefaction and ammoniacal change is more marked than in healthy urine. Slight haemorrhage occasionally occurs; but when it is abundant, and influenced by movement, it probably depends on the existence of a renal calculus. Microscopical examination reveals epithelial cells derived from the tubules, hyaline casts, and casts made up of pus cells, imbricated epithelium from the pelvis, and sometimes fragments of renal tissue, triple phosphate crystals, and various forms of micro-organisms.

Pyelonephritis, associated with renal distension, is characterised by the presence of a renal tumour and perhaps by intermittence of the pyuria. The swelling is generally smooth and rounded, occupying the loin and yielding a resonant note on percussion in front. There is pain and tenderness; and very often perinephritis supervenes, increasing the size and firmness of the swelling. With the appearance or increase of the tumour there may be disappearance or diminution of pus from the urine; and when the tumour subsides, pus reappears in increased quantity, and the symptoms are temporarily alleviated. The further course of the case may be that of pyonephrosis; or of renal abscess complicated by secondary calculi, with pain and haemorrhage on movement; or of perinephritis either of the sclerosing or suppurative variety. The symptoms will be accentuated if the opposite kidney be implicated.

Diagnosis.—When no tumour exists, but only constitutional symptoms with pyuria, the disease may easily be confounded with chronic cystitis, or with tuberculosis of the urinary organs. In chronic cystitis there would probably be no polyuria, the urine would be alkaline and glutinous, and the distribution of pus in the urine would be less uniform than in pyelonephritis.

Tuberculous disease of the kidney may be associated with recognisable lesions in other organs, and the characteristic bacilli may be found in the urine. Haemorrhage is more frequent, and the febrile exacerbations are less marked. The rapid failure of the patient's strength is sometimes an important sign. When a tumour is present, the disease may simulate tuberculosis or hydronephrosis; in the latter case fever and septic manifestations are usually absent.

Prognosis.—Attacks of the primary affection due to irritant drugs, such as cantharides, or to cold, are usually transitory. Those that follow disease of the bladder or other pelvic organs, those affecting both sides, and those that develop acutely, are more formidable, threatening death by urinary toxæmia. Chronic cases with free discharge of pus have the most extended course, lasting often for months or years; and the outlook depends largely on the condition of the digestive organs.

The most formidable cases are those with retention of pus, which

distends the renal pelvis and destroys the parenchyma, leading to toxæmia or to the rupture of the sac and the establishment of a fistula.

Treatment.—In suppurative nephritis and pyelonephritis the treatment is essentially the same as that for acute or subacute nephritis without suppuration. Every precaution should be taken to prevent their recurrence. Any obstruction to the outflow of urine, or any incapacity to empty the bladder completely, should be remedied or counteracted; stricture of the urethra should be dilated or divided, vesical calculus removed, and the effects of enlarged prostate combated by early and regular catheterism or prostatectomy. If chronic cystitis exist, daily irrigation of the bladder will be necessary to obviate decomposition of the urine and to restore the mucous membrane to a healthy state. The impaction of a stone in its course between the kidney and bladder calls for its removal either by the bladder, loin, or abdominal route; according to its position in the ureter. Confinement to bed is necessary as soon as inflammation has once set in.

With the object of avoiding the severe and dangerous onset of pyelonephritis, as well as the slighter forms of urinary fever, catheterism should never be employed except when the patient, during and for some hours after the introduction of the instrument, is in a warm and equable temperature, preferably in his bed.

The bowels should be kept well opened, and for this purpose warm abundant enemas are of special service.

The diet should be light and moderate, and should consist chiefly of fish, milk, chicken or game, light farinaceous or milk puddings, and well-cooked vegetables; uncooked vegetables and fruits as well as butcher's meat should be avoided. Stimulants should be taken, if at all, in very small quantities; and if, during their administration, the pulse is quickened, the temperature raised, or the urine becomes more purulent, they should be discontinued at once.

Liquids should be taken in moderate quantity only, if the amount of urine excreted be abnormally large; but where cystitis exists, and much mucus is passed in the urine, ordinary diluents and 5-gr. doses of cystamine or urotropine twice or three times a day are useful in slaking thirst and improving the state of the urine.

Little can be said in favour of medicines; a mixture of 1 grain of quinine with 5 min. of tincture of opium in mucilage has proved of benefit in some cases; and 5 grains of salol or baborate of magnesium in doses of $\frac{1}{2}$ -1 dram have been given, with a view of controlling the septic changes in the urinary tract. When constipation exists, and a large quantity of urine is excreted, I have seen great benefit accrue from a few doses of ergot of rye. This drug, by acting upon the involuntary muscle-fibres of the gut, overcomes the constipation, and by its influence on the coats of the blood-vessels constricts and gives tone to the renal circulation. The constipation, flatulence, atony of bladder, and general arterial and muscular feebleness, suggest remedies which will give contractile force to the muscular fibres of the viscera.

When the febrile attack takes the remittent form, 5 grains of quinine in 1 oz. of lemon juice, and $\frac{1}{2}$ dram to 1 dram of liquor morphinae, are sometimes very efficacious in checking the rise of temperature.

Traube obtained good results from injections into the bladder of acetate of lead, from $\frac{1}{2}$ - $1\frac{1}{2}$ gr. in 4 oz. of distilled water, and the internal administration of pills of tannic acid (1- $1\frac{1}{2}$ gr.) every two hours. He recommends both of these remedies because of their antiseptic and antiphlogistic action.

Drugs, such as tannin, alum, acetate of lead, and perchloride of iron, which act as astringents upon the blood-vessels of the mucous membrane, and so lessen the excessive secretion of mucus, have been recommended, and certainly deserve fair trial. When the urine is alkaline, benzoate of ammonium in 10-gr. doses may be tried, and often with benefit.

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VIII. ABSCESS OF THE KIDNEY is one of the varieties of suppurative disease of the kidney. It is not intended here to refer to cases of minute and scattered points of suppuration, the origin of which may be infection carried by the ureter, blood-vessels, or lymphatics, or to miliary abscesses due to the irritation of calculous matter in the kidney. What we have now to describe is suppuration resulting in one or more abscesses of considerable size in the substance of the kidney.

Etiology.—It must be stated at once that renal abscess of large size, involving the greater part or even the whole of the kidney, occurs as the result of the fusing together of a large number of miliary abscesses. Suppuration of this kind may be limited to one kidney, the other being quite unaffected. Metastatic and secondary abscesses of large size may be also formed otherwise. Thus, in pyaemia, or in cases of embolism derived from infective endocarditis, instead of a number of minute and scattered emboli followed by minute and scattered points of inflammation and suppuration, one large vessel may be obstructed by an embolus and a large abscess may ensue. Sometimes, as a result of stricture or other disease of the lower urinary organs, a circumscribed abscess may form in the tubular substance of the kidney. Wounds, contusions, and lacerations of the kidney, and kicks, blows, or falls, involving the loin or renal region on the front of the abdomen, are occasional causes of suppuration

and abscess of the kidney. More usually when renal abscess occurs as the result of injury to the loin, whether attended with immediate injury to the kidney or not, the suppuration of the kidney has been preceded by suppuration in the circumrenal cellular tissue; so that the abscess involves the kidney by spreading from without, and is not primarily a renal abscess. Injuries which cause obstruction in the renal pelvis or ureter are especially likely to be followed by more or less suppuration of the renal tissue; moreover, injury to the kidney, from its tendency to excite the formation of renal calculus in the injured organ, may be in this way an indirect cause of renal abscesses of large size. A calculus which originates in a renal tubule, or one which becomes more or less shut off by inflammatory adhesions from the general cavity of the pelvis of the kidney, is the most likely to give rise to an abscess in the substance of the kidney; the impaction of a stone in the renal pelvis or ureter leads more frequently to calculous pyelitis and thus to pyonephrosis.

Foreign bodies other than calculi may give rise to a large renal abscess. A piece of bone, a fragment of clothing, or a bullet may gain entrance to the kidney; and, instead of becoming quietly encysted, or passing through the natural channels out of the body, may give rise to extensive suppuration in the organ in which it rests.

A kidney containing an abscess said to have been caused by cantharides, is preserved in the Museum of the Royal College of Surgeons; death occurred in three weeks.

Pathology.—Circumscribed abscess usually affects one kidney only. There may be one or several abscesses in the same organ. In size, they vary from that of a cherry-stone or a hazel-nut to that of an orange. They may communicate with the pelvis of the kidney, or through the capsule with the peri-renal cellular tissue. When they open through the capsule they lead either to a circumscribed perinephric abscess, or to diffused and burrowing retroperitoneal suppuration. When they open into the renal pelvis they may empty themselves partially or entirely through the ureter and bladder. When two or more abscesses affect the same organ they may communicate with one another or remain distinct; and one may discharge in one or other direction, the others remaining unopened. This isolation of several abscesses should be borne in mind in exploring the kidney for suppuration.

In a very considerable number of specimens of renal abscess, the whole organ, including the pelvis, is involved; and very little, if any, renal substance is left. It is not easy in some of these cases, especially when the ureter of the affected side is pervious and the opposite kidney and lower urinary organs are not diseased, to say whether the morbid process began as a pyonephrosis or as abscess in the renal substance. It is undeniable that many of the cases reported as renal abscess are really far-advanced cases of pyonephrosis.

Symptoms.—These may be either acute or chronic. In the acute cases there is pain in the region of the diseased organ, with fever and rigors. The rigors are sometimes marked and frequent; at other times

one or two only occur throughout the course of the disease, and these at uncertain and irregular periods.

Haematuria often precedes the formation of abscess when the cause is trauma. The absence of pus from the urine is no test; in many cases there has been none whatever throughout. In other instances, if the abscess have broken into the pelvis of the kidney, pus, it may be in large quantity, will be seen in the urine. If a tumour has been formed in the loin, the discharge of pus by the bladder will probably be followed by diminution or subsidence of the tumour. It is not often, however, that any tumour perceptible during life is formed by a circumscribed abscess of the renal substance. If a tumour do exist, with the history or symptoms suggestive of suppuration, dilatation of the cavity of the kidney may with fair certainty be predicted; or else it may be that the whole organ is in a state of general inflammation with several foci of threatening or actual suppuration.

When the abscess is chronic in character, it may form without causing any definite symptoms. Indeed, the abscess may be found at the necropsy without having caused a suspicion of its existence during life. In some cases, however, loss of appetite, nausea, occasional vomiting, general impairment of health, occasional chilliness and rigors, obscure aching, sometimes severe sickening pain in the loin, gradual emaciation and increasing sallowness or duskiness of skin indicate some grave disorder, but do not point with any distinctness to its nature.

In acute cases a fatal termination may occur in a fortnight to three weeks. The cause of death will most probably be typhoid prostration. Occasionally, however, the abscess bursts into the cellular tissue, the intestine, or the renal pelvis or ureter; and then life may be prolonged for a time, till ended by exhaustion or general sepsis.

Possibly recovery may ensue; in some cases it is pretty certain that the contents of the abscess, instead of escaping in any of the directions mentioned, become inspissated and remain quiescent for the rest of life.

Treatment.—The treatment of the early stages of a renal abscess is the judicious administration of subcutaneous injections of morphine, the local application of anodyne fomentations, followed by an incision down to and into the kidney, and either the evacuation of the pus and the erosion of the abscess-walls, or the excision of a wedge-shaped piece of the kidney. If caused by renal calculus, the treatment suitable for the varying phases of this disease will be required. In any case in which there is clear indication of a renal abscess, the pus ought to be immediately evacuated through an incision in the loin.

Indeed, in the absence of a tumour, but with the history and symptoms suggestive of suppuration, to make an exploratory incision down to the kidney is the right treatment. If, when the kidney is punctured, pus is found, it is not sufficient to evacuate it with a trocar and cannula; a free incision should be made into the abscess, and the wall of the abscess cavity, if a large one, should be stitched to the edge of the wound. When the finger in the kidney enters a space which does not communicate

with the general pelvic cavity of the organ, or does so only by a small orifice, the rest of the surface of the organ should be carefully manipulated, and if fresh pus be found, a second or even a third incision of the renal substance should be made so as to open the other abscesses. If the kidney be very much destroyed, it may be best to remove it at once through the lumbar incision.

The kidney is very much more tolerant of interference than it is generally believed to be; and the fear of haemorrhage is reduced to a minimum by restricting incisions to the periphery. In cases in which nephrotomy has revealed either local or disseminated disease with areas of healthy parenchyma between the foci, and especially if there be a probability of bilateral distribution, it is better, instead of removing such a kidney, to treat each focus independently by scraping or by the excision of a wedge. This plan may be resorted to in cases of multiple abscess or of multiple tuberculous deposit, or suppurating cysts, and may be combined with nephrolithotomy. When operative measures have to be taken in connexion with the second kidney, the surgeon has a much freer hand if the active and healthy part of the organ first operated upon is still discharging its function.

It is remarkable, too, what a powerful influence on the excretion of urine even small portions of renal substance exert, and what a capacity for recovery patients evince after the removal of some condition interfering with the functional activity of their kidneys, such as pressure upon or obstruction of the ureter. Evidence of this is met with in the quantity of urine (often of low specific gravity, it is true) passed after relief of hydronephrosis, where the organ has been distended and thinned to a mere capsule; and not infrequently at necropsies mere remnants of kidneys, weighing but a few drams, are found, which had been active and serviceable for many years between the occurrence of acute disease and the ultimate death of the patient.

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IX. RENAL FISTULAS.—Fistulas which communicate with the kidney and pelvis of the kidney.

Causes.—Renal fistulas are caused, in the great majority of cases, by calculi in the pelvis of the kidney or in the ureter. Other causes are gun-shot, punctured, and incised wounds, injuries inflicted by surgical operation, and abscess of the kidney. The opening into the cavity of the kidney is usually single and connected with the posterior aspect of the organ. Renal fistula may open at the loin or groin, into the colon or duodenum, into the pleural cavity or lung, or into the peritoneum. It is comparatively rare for a fistula to open into the peritoneum. If the fistula be the result of a wound or a ruptured hydronephrotic cyst, urine, sometimes in large quantity, will escape from it; if the effect of pyonephrosis due to ureteral obstruction, pus will be mingled with the urine; if caused by the conversion of the kidney into a tuberculous abscess cavity the discharge will consist of pus and broken-down tuberculous material.

Renal Fistula opening in the Loin.—When fluid of a urinous character escapes from a fistula which followed suppurative nephritis or injury to the kidney, the diagnosis of the renal origin of the fistula is certain. It must be remembered, however, that a lumbar fistula, without communicating with the kidney at all, may be the result of disease in the ureter, the bladder, or even the urethra.

Treatment.—The skin around the orifice must be kept clean, and free from irritation. If, after a fair length of time has been allowed for spontaneous closure, the fistula persist, an incision, such as that employed for laying open any sinus track and for vivifying callous edges or removing spongy granulations or calculous deposits, must be made. The

free use of the respiratory is sometimes followed by the complete closure of the track.

If the other kidney be sound, and a permanent fistula communicating with a diseased organ threatening the life and sacrificing the comfort of the patient resist other treatment, the best plan is to perform nephrectomy ; and if, owing to dense adhesions, nephrectomy is impossible or only possible by means of subcapsular piecemeal nephrectomy (*morcelement*), it will be better to ligature the renal vessels through the transperitoneal route, as was successfully done by Major M. P. Holt. Ligation of the renal vessels for the cure of persistent urinary renal fistula is quite a well-founded operation, since it has, years ago, been proved clinically and by experiments that ligature of these vessels, or complete obstruction of the ureter, rapidly results in total disappearance of the kidney as a secreting organ.

Renal Fistula opening into the Stomach.—This is of extremely rare occurrence. There is much uncertainty as to the genuineness of the symptoms and the accuracy of the diagnosis in some of the cases. In one case of communication of the left kidney with the stomach, pus, urine and calculi are said to have been vomited. In a case of gastro-renal fistula due to tuberculous pyelonephritis, admitted under my care into the Middlesex Hospital in 1884, there was a history of "inflammation of the bladder" and of "pus in the motions," as well as in the urine. There were four sinuses in the back discharging pus. Careful examination of the chest and abdomen disclosed nothing abnormal. No physical signs of pelvic cellulitis or circumrenal abscess could be made out. Complete anuria preceded death. On post-mortem examination the only communication between the kidney and the gastro-intestinal tract was a fistula of the diameter of a crow-quill, opening into the left margin of the great curvature of the stomach.

Renal fistula communicating with different parts of the intestine and renal fistula opening into the lung are very rare. Prompt surgical treatment might in some instances have prevented their formation.

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X. URINARY FEVER.—This term is used to group together cases of more or less transient attacks of fever which depend on impressions produced upon the urethra either by the passage of instruments or by some other cause. Such an attack may follow the mere passage of a catheter along a healthy urethra into a healthy bladder ; or its use for the first time at the commencement of catheter life by an elderly man with enlarged prostate ; or it may be produced by the performance of some simple operation for stricture of the urethra ; or by the passage along the urethra of a blood-clot, a renal calculus, or a quantity of oxalate of

lime or uric-acid gravel. I have also known such attacks to occur in a female after an operation for vesico-vaginal fistula, in a man immediately after the perforation of the floor of the urethra by epithelioma of the penis during an act of micturition ; and in another man by the escape of a few drops of urine through an old fistula of the urethra situated just behind the corona. It would seem that it is only in some persons and owing only to some impressions on the mucous membrane of the urethra or bladder that these attacks of fever occur. It is remarkable that urinary fever is scarcely ever, if ever, caused by a severe injury to the urethra or bladder, or by passing a catheter to relieve painful retention of urine in the young or middle-aged subject. The impressions take effect upon perfectly healthy organs, but are more likely to do so on organs which are already the seat of disease. The presence of renal affections, enlarged prostate, chronic affections of the bladder, and urethral stricture dispose to the occurrence of the fever, which too is often of greater severity and importance under such conditions than when occurring in the healthy subject. Persons who have had malaria or who are prone to "aguish attacks" are very apt to suffer an attack of urinary fever on the least interference with the urethra.

Etiology.—There are two principal views as to the pathogenesis of urinary fever. One is that the affection is entirely of nervous origin, excited by the irritation of the urethral nerves causing a far-spreading effect which is primarily felt by the kidneys, and then by the entire system. The second view regards all these cases as caused by an infection of the genito-urinary tract followed by absorption of toxins.

It is probable that a large number of cases do depend upon infection, and are due to an invasion of the urinary tract by *B. coli*; others, however, it is difficult to explain in this way. It is most likely that in some the nervous element plays the chief if not the sole part in their causation. However careful a surgeon may be in every detail of instrumentation, attacks of urinary fever do occur after the most simple and apparently most trivial proceeding; moreover, the same person may suffer at one time and not at another, although the character and conditions of the urethral impressions are precisely the same on each occasion. In every case of urinary fever cultures of the urine should be made.

Pathology.—Congestion of the kidneys is the marked pathological feature in all the forms of urinary fever. The degree of congestion varies from slight, mottled redness to the most intense engorgement of the renal vessels, extravasation of blood into the renal tubules, and excessive softness and friability of the renal substance. Complete absence of congestion after death is no criterion of the state during life, if only a few hours have passed between the commencement and the termination of the attack. After death the renal vessels rapidly empty themselves, and the blood returns to the large abdominal veins, unless the congestive state had been long maintained prior to death.

When death has taken place not before the third day the microscope has shewn a considerable exudation of small round cells into the inter-

tubular tissue throughout the kidney, whereby both blood-vessels and renal tubules have been compressed, and thus the blood-pressure in the Malpighian tufts has been lowered whilst the urinary tubules have been partly obstructed by being compressed. In this manner complete suppression of urine is brought about. When this condition exists the kidneys are large, tough, and pale—they are, in fact, anaemic, and without, therefore, a trace of congestion.

In fatal cases of the "intermittent" fever the kidneys have usually become the seat of suppuration, though this may only be discoverable by the microscope. Fatal cases of so-called catheter fever, in which no definite ascertainable structural lesion adequate to account for death has been found in the kidneys, are really cases of urinary septicaemia or sapraemia due to cystitis, and the absorption of toxins from pus and decomposing mucus and putrid urine, and are not cases of urinary fever.

Symptoms.—The attack of fever may take the form of a single transient paroxysmal seizure, and may be over in from three to six hours; or of recurring paroxysms of fever, one succeeding the other at short intervals of from six to eighteen hours, and the whole attack terminating at the end of from two to four or five days; or, but much more rarely, and usually only when chronic interstitial nephritis exists, the intervals between the paroxysms are of considerable length and may extend over several weeks or even over four or five months, the patient between the febrile attacks being in a state approaching, though not actually amounting to, normal health. The paroxysm of fever is always ushered in by a rigor which may be slight and little more than a sense of chilliness and attended with a rise in temperature of one or two degrees only. This, with perhaps a little nausea, and a feeling of faintness and headache lasting for a few hours may constitute the entire attack.

On the other hand, the rigor may be most violent and last for half an hour, the temperature rising to 105°, 106°, or 107° F. As a rule the intensity and duration of the attack are proportionate to the severity of the rigor. The rigor is followed by a dry, burning skin, dry tongue, flushed face, and accelerated breathing and pulse; and this stage in turn is succeeded by one of profuse perspiration, during which the temperature is frequently below normal. Delirium may occur in the hot or cold stage, but scarcely ever in the sweating stage. Vomiting, headache, pain in the back and limbs, and injection of the conjunctiva are the other prominent symptoms of a severe seizure. The urine may be completely suppressed; more often it is excreted in small quantities and is then often turbid and contains albumin and blood. This is the *transient form*. Such an attack, even when most severe, if it occurs in a person with healthy urinary organs, will be recovered from and the patient will feel in his usual health within thirty-six or forty-eight hours, but if it affects one who is very infirm, weakly, or unhealthy, death may take place within the same or a shorter length of time.

In the *recurring form* the symptoms are the same as in the transient

form and vary in degree to a similar extent. The difference is that instead of passing off after one seizure there is a quick succession or repetition of rigors, elevations of temperature, and sweatings. The temperature rapidly rises until, by the end of the rigor or shortly after, it reaches some point between 102° and 107° F.; it then declines by stages, and within six to eighteen hours will be normal or below. A second paroxysm of rigor and rise of temperature and subsequent subsidence with more or less sweating occurs; and a third or a fourth similar paroxysm follows in due course. Occasionally the rigor may be absent in the second or subsequent seizures. These "recurring" attacks rarely last less than two to three days, and they may extend over four or five days or a week, during which two, three, or four seizures may happen within the first forty-eight hours. Throughout the whole course of a "recurring" attack the patient looks and feels excessively ill; but with the ultimate reduction in the temperature the other symptoms pass off, the appetite returns, the bowels act naturally, the urine is excreted in normal quantity, ceases to contain blood or albumin, and its specific gravity and other characters become normal—in fact, the patient is well again.

Both the "transient" and the "recurring" forms of fever may be excited again and again in the same person by a renewal of the cause of excitation, or the "transient" form may be induced at one time and the "recurring" at another.

The *intermittent form* is rare except in persons with chronic interstitial nephritis, and although it appears in many cases to be directly excited by the simple passage of a catheter, it usually depends in reality upon septic absorption from some part of the urinary tract, and is occasionally associated with effusions into joints and other septicaemic symptoms of a mild character. As a rule the termination is favourable; the intervals between the intermittent seizures lengthen, and after three, four, or more accessions of fever recovery is established. When the fever is going to take an unfavourable course it becomes continuous, and the symptoms of interstitial nephritis supervene. At the autopsy the kidneys will be found inflamed and probably suppurating. Like the "transient" and "recurring" forms of urinary fever it may be either slight or severe, subacute or acute. But whereas in the other two forms the feverish attacks come on suddenly and within a few hours after the provocation, and the patient is very ill throughout the attack, and whereas a relapse does not occur except as the result of a fresh provocation; in the intermittent form, on the other hand, the attack comes on insidiously some days after the use of an instrument, or exposure to some other cause of irritation, its onset is not always marked by a rigor, relapses take place without any fresh provocation from without, and the patient has intervals of comparatively fair health between one febrile period and another.

It is this form of urinary fever which is so often described as "aguish," without the least suspicion being aroused either in the patient or his doctor that the true cause resides in the urinary passage. I have

known, for example, a physician who suffered from these intermittent feverish attacks for thirty-six years without ever having considered that a penile stricture and a narrow urethral fistula which he also had, could be or had been in any way the cause of them. I first saw him professionally in one of these attacks, when several of his joints were swollen from simple effusion into their synovial cavities. I pointed out to him privately the cause, as I believed, of the whole of his trouble, and he followed my advice as to its treatment; his regular medical attendant, however, whom the patient wished should not be informed of the stricture and fistula, continued to regard the illness, just as others had considered the former attacks, as "of a gouty nature." Inquiry in every doubtful case of "aguish attacks" in males should always be made as to the condition of the urethra, and not unfrequently a stricture or some other old-standing disorder will be found. Swelling of one or more of the joints, especially of the knees and ankles, and of the sheaths of tendons, or oedema of the lower limbs is sometimes met with in this form of urinary fever. The swelling of the joints and tendon-sheaths is due to simple effusion of synovia without, as a rule, redness, heat, or tenderness, although some pain may be felt on movement. The fluid rarely becomes puriform. These joint cases are very chronic, three, four, and five months being required for their cure.

Diagnosis.—From *interstitial and suppurative nephritis* the "transient" and "recurring" forms of urethral or urinary fever are to be distinguished by the sudden and rapid development of the symptoms, and the short duration of the attack. The "intermittent" fever is more likely to be mistaken for interstitial nephritis, a disease indeed upon which it is very prone to be engrafted. From *ordinary septicaemia* the short and commonly favourable course of the attack will distinguish the "transient" and "recurring" fever; and the intervals of fair or good health between the attacks will mark off the "intermittent" fever. From *uraemia* the diagnosis may be much more difficult, but the absence of coma, drowsiness, and convulsions serve to exclude *uraemia*. From *gonorrhœal rheumatism* urinary fever will be distinguished by the discovery of the gonococcus in the one and its absence in the other; otherwise there are many points of resemblance. The history of the onset, the paroxysmal attacks, and the good health in the intervals between them serve to characterise the "intermittent" fever—the only form for which *gonorrhœal rheumatism* can be mistaken.

Prognosis.—It is exceptionally rare for any serious termination to follow either of the forms of urinary fever. Even though the excretion of urine may be suppressed for many hours, recovery under appropriate treatment is the rule. Death, however, has occurred in each form of the disease at periods varying from six hours or less in the "transient" type, to two or three weeks or more after the onset of an "intermittent" attack.

Treatment.—The prophylactic treatment is purely surgical, and though of the very highest importance it would be out of place to do

more than mention it here. When the joints are affected in the "intermittent" cases, careful surgical treatment of them is demanded. As soon as a rigor occurs it is essential to put the patient to bed and to keep the skin warm and promote perspiration. Hot weak tea and other hot diluents should be partaken of freely, and great benefit is very often derived from one good dose (an ounce or an ounce and a half of brandy or rum added to the tea or taken in hot water). If diarrhoea is present, as it sometimes is, it should not be stopped, especially if partial or complete suppression of urine complicate the fever. Sweating and diarrhoea are the two chief means of eliminating those deleterious products which the kidneys are no longer removing from the blood. Vomiting may also be assisted or promoted in cases of suppression; in one of my cases, in which the suppression had lasted forty-three hours, the vomit contained 2·7 per cent of urea; and as a large quantity of fluid was ejected from the stomach and the kidneys were quite healthy the patient did not become comatose, and made an excellent recovery.

Morphine, if the kidneys are healthy, by increasing the action of the skin, helps to relieve the congested renal blood-vessels. In cases of suppression without organic renal disease I have seen most marked improvement follow the subcutaneous injection of $\frac{1}{20}$ gr. of atropine, with $\frac{1}{2}$ gr. of morphine—exhausting vomiting was checked, sleep was induced, perspiration promoted, and 4 ounces of urine were excreted at the end of six hours from the time of the injection. Pilocarpine increases the action of the skin, but its effect on the kidney is uncertain. The diet should consist chiefly, if not entirely, of milk; solid food cannot be taken during the height of the fever. Beef-tea and meat extracts are unsuitable during the functional inactivity of the kidneys. Lime water will correct acid fermentation in the stomach, and Vichy water and barley water with milk form very useful drinks. Saline aperients are the best if the bowels are costive, and enemas are often of great use. Nutritive enemas may be required if vomiting is prolonged and excessive. Quinine, aconite, and iron are the best and most suitable drugs. Five to ten grains of quinine in lemon juice combined with $\frac{1}{2}$ to 1 ounce of brandy, and half a dram of liquor morphinae, given at once, and repeated in two hours if the rigor has been severe and the temperature keeps above 100° F. often give very satisfactory results in the "transient" and "recurring" types of cases when there is not suppression of urine. In the "intermittent" type milk and fish diet, mineral acids with bark or quinine (or, better still, tincture of iron), and warm clothing are the essential points of treatment. Cystamine or urotropine should be given regularly and continued for some time in cases of bacilluria.

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XI. NEPHRECTASIS OR RENAL DISTENSION occurs in three forms, namely, hydronephrosis or distension with urine, pyonephrosis or distension with pus, and haematonephrosis or distension with blood. In pyonephrosis and haematonephrosis the amount of pus or blood respectively varies considerably in proportion to the amount of urine mixed with the pus or blood. The cause and mode of distension is the same in each class of case, and is mainly the result of hydrostatic pressure plus the extensibility of the renal structures on the one hand, and mechanical obstruction on the other. The obstruction must be either incomplete, intermittent, or of gradual development; for it has been shewn clinically and experimentally that a sudden complete obstruction leads to rapid atrophy and ultimately to complete disappearance of the affected kidney.

A. Hydronephrosis.—This name is given to over-distension of the kidney with urine, the result of mechanical obstruction, no matter whether the cause be in the urethra, bladder, or ureter. Probably one-third of the cases of hydronephrosis in which a palpable tumour is formed have a congenital origin.

Congenital Causes.—Twistings, undue obliquity, contractions, and other anomalies of the ureter. This duct is in some cases a mere fibrous cord; or its vesical orifice may be of pin-hole size; or minute cysts may develop in its mucous membrane; or the angle of its junction with the kidney may be so acute as to impede the descent of the urine. Cases of double hydronephrosis of congenital origin are not very uncommon.

Acquired causes are cancer of the pelvic organs, fibromyoma, pelvic inflammation with contraction of the cellular tissue. On account of its frequent dependence on pelvic disease and upon movable kidney, hydronephrosis is very much more frequent in women than in men. Calculus is a frequent cause, either by being impacted in or by causing ulceration followed by contraction of the duct. Other causes are tumours, inflammation, or ulceration of the bladder followed by contraction of the vesical orifice of the ureter. A papilloma or fibroma of the bladder and prolapse of the vesical orifice of the ureter, and a calculus lodged in a pouch close to the vesical orifice or in the duct itself as it passes through the vesical wall, are other causes of unilateral hydronephrosis. Compression of the ureter by enlarged lymphatic glands, adhesions or bands of fibrous tissue, induration and condensation of the surrounding cellular tissue and other causes of pressure upon the ureter produce it. Hydro-

nephrosis may affect both kidneys or only one, or may be limited to a part of one kidney. Stricture of the urethra, phimosis, enlarged prostate, flexions and prolapse of the uterus, and uterine tumours are common causes of double hydronephrosis. When distension is limited to one portion only of the kidney, it is generally due to obstruction in one part of a double renal pelvis, or to a double ureter one only of which is blocked. The proportion of cases in which hydronephrosis produces a palpable abdominal tumour is very small compared with the frequency of the disease.

Pathology.—The pelvis of the kidney first becomes converted into a spheroidal sac, then the calyces are widened and stretched in every direction, and at length the capsule of the organ is expanded, and what remains of its cortical and medullary substance becomes still further compressed and absorbed until nothing is left but a loculated cyst, the septa of which are inextensible. The size of the hydronephrotic sac may not exceed that of a normal kidney ; it may even be smaller ; or, on the other hand, it may be sufficiently large to form a swelling occupying a great part of the abdominal cavity. The contained fluid is water, holding a larger amount of sodium chloride than exists in urine and a few epithelial cells. Its quantity is sometimes enormous, amounting to several gallons. Urea is often all but absent. The reaction is acid or neutral, and the fluid may be dark in colour and colloid in consistence. When the seat of obstruction is in the lower urinary organs the ureter is dilated, and commonly the change is bilateral. When the obstruction is in the urethra, pyogenic infection is more common, and pyonephrosis succeeds to hydronephrosis. As regards the communication with the bladder, it may be open, closed, or valvular.

My experience in operations on the kidney has led me to classify cases of hydronephrosis into (i.) Simple hydronephrosis with atrophy without expansion ; these are the small, flaccid, shrivelled kidneys. (ii.) Simple hydronephrosis with atrophy and expansion ; these often enlarge into huge cysts. (iii.) Hydronephrosis with atrophy of the pyramidal, and thickening and sclerosis of the medullary substance ; these kidneys have generally been inflamed, and are prone to suppurate.

Symptoms.—Hydronephrosis may occur at any age, and is twice as frequent in females as in males. When the dilatation is insufficient to give rise to a tumour, there are generally no signs characteristic of hydronephrosis. Out of a series of 142 cases at the Middlesex Hospital an abdominal tumour was formed in but very few. In some advanced cases in which no tumour exists, thirst, pain in the back, frequent micturition, partial, total, or intermittent anuria, and obscure or pronounced abdominal pains are present.

A hydronephrotic tumour is dull on percussion, sometimes lobulated in contour, and frequently fluctuates. It has all the characters of a renal tumour, being situated in the flank, pressing the ilio-costal parietes backwards and outwards, having the colon in front of it, and the small intestine either in front or thrust over to the opposite

side of the abdomen, according to the bulk of the swelling. If of no great size, it may be painless; if large, it may give rise to excruciating suffering.

When it arises from some innocent cause, such as pregnancy or uterine flexion, its formation is unattended by any constitutional or local disturbance; but when from some painful cause, such as impacted calculus, or sudden kinking of the ureter, the symptoms incidental to the particular condition will occur before the tumour makes its appearance, and may cause it to be overlooked.

There are instances of the tumour *intermitting*, that is, being prominent at one time and not distinguishable at another, the disappearance of the tumour being sometimes associated with polyuria, the urine being accompanied by blood, pus, or mucus. In some cases constipation results from pressure on the colon; in others, no recognisable symptoms occur till uraemia sets in.

Diagnosis.—When of moderate size, the tumour has to be distinguished from renal or perinephric abscess and perinephric extravasation. When it forms a palpable tumour, it may be mistaken for pyonephrosis, or for a hydatid or serous cyst of the kidney, liver, or spleen. When of great size, it may simulate ascites or parovarian cystoma. If the subsidence of the tumour is followed by an increase in the outflow of urine, the diagnosis of its hydronephrotic nature is clearly indicated. Perinephric abscess is quicker in its course, and excites much more pain and constitutional trouble in its early stage. Between hydronephrotic and pyonephrotic tumours the diagnosis is often impossible and indeed immaterial, and depends upon the amount of pus in the urine and the presence or absence of the constitutional signs of suppuration. Purulent urine, rigors, and fever indicate pyonephrosis, as a rule; but such diagnostic symptoms may be absent. Hydatid and serous cysts of the kidney are best diagnosed by their history.

From ovarian tumours the diagnosis is often very difficult. These are, as a rule, more mobile than renal cysts, and enlarge upwards from the pelvis, not forwards from the loin. Moreover, the intestines are behind an ovarian and in front of a renal tumour. When the tumour is renal, the uterus is neither displaced nor fixed. In the case of an ovarian or parovarian cyst, on the other hand, it is displaced upwards and to one side.

Prognosis.—This depends in great measure upon the distension, but chiefly upon whether one or both organs are involved. If only one kidney is affected, and the tumour not large, life may be indefinitely prolonged. There is always, however, the fear that calculus or other disease of the opposite kidney may cause death by suppression of urine or uraemia, or that suppuration may occur in the cyst. If the distension increase, death may result from pressure on neighbouring organs, rupture into the peritoneum, or suppression of urine.

Treatment.—Medical remedies are of no avail. Surgical measures should be directed against the cause of the hydronephrosis, whether it is

mobility of the kidney or a tumour or other extra-ureteral pressure on the tube, and whether it is situated in the abdomen or pelvis. When the cause is an abnormality of the ureter at the pelvis of the kidney, and a fair amount of secreting renal tissue remains, a plastic operation for the removal of the obstructing cause is demanded. When the amount of renal parenchyma remaining is very little, or the condition of the patient gives no encouragement to hope for good repair following a plastic operation, nephrotomy with drainage or nephrectomy must be practised. After nephrotomy for hydronephrosis search should be made with the finger through the lumbar incision with the object of detecting a stone, and the ureter should also be tested by passing a long probe or small sound along it from the interior of the kidney downwards. Lumbar nephrectomy is required when the kidney is so much damaged as to be incapable of performing its function, or when there is a free continuous discharge from the loin after treatment by nephrotomy; except, of course, in cases in which the opposite kidney is defective.

Congenital Hydronephrosis.—In by far the larger number of cases of hydronephrosis found in the fetus and new-born, both kidneys are involved, the most common cause being imperforate urethra. It may be due to minute cysts, or to membranous septa in the urethra; or to cysts in the ureter or pelvis of the kidney. The subjects of this disease may be born dead, or may live for a few weeks, months, or even years. The urine removed from some of the cases of congenital hydronephrosis has contained little or no urea. The size of a hydronephrotic fetus has proved a serious impediment to labour in several cases, and has rendered parturition impossible, until the abdomen of the child has been reduced by tapping.

Congenital hydronephrosis is frequently associated with some other congenital deformity, such as hare-lip or club-foot.

These cases prove that the secretion of urine goes on to a very considerable extent during the latter half of intra-uterine gestation; and that when any obstacle to the outflow of urine exists, the same pernicious effects of distension of the bladder, ureters, and kidneys occur before birth as are commonly known to arise from phimosis, urethral stricture, calculus, and other causes of obstruction after birth.

B. Pyonephrosis implies dilatation of the pelvis and calyces of the kidney with pus, or pus and urine. In advanced cases the suppuration and dilatation extend beyond the calyces, and go on to compression and disintegration of the pyramidal and cortical substance, converting the organ into a large loculated sac, the nature of the contents of which depends upon the cause of the obstruction.

Hydronephrosis becomes pyonephrosis as soon as suppuration occurs; and therefore the causes of pyonephrosis are similar to those which generate hydronephrosis. When an obstruction causes pyonephrosis at once, it is more complete in its character, and more rapid in its irritative effects upon the kidney, than when it causes hydronephrosis first. In some cases of pyonephrosis, the pyelitis, instead of following,

has preceded the obstruction. A small mass consisting of blood-clot, inspissated pus or mucus as a result of pyelitis, or the detritus from a calculus, new growth, or tuberculous deposit may block the ureter, and so lead to distension with urine and pus; to which may be added, in some instances, blood, mucus, phosphatic deposit and detritus from the disorganized kidney or new growth.

Etiology.—The most frequent cause of pyonephrosis is calculous pyelitis; indeed, renal calculus is so largely in excess of other causes that it has been implied, if not explicitly stated by some writers, that pyonephrosis and calculous pyelitis forming a renal swelling, are one and the same thing. This, however, is not the case. Definite and even fatal pyonephrosis may exist without giving rise to any palpable tumour during life, and without doubt may be caused by many conditions other than stone. Such other causes are pyelitis from extension of septic inflammation from the lower urinary organs, arising in stricture, gonorrhœa, spinal disease, and cystitis however produced; obstruction of the ureter by pressure or infiltration of tumours or inflammation in the pelvis; tuberculous and pyaemic deposits in the kidney or renal pelvis; the presence of such parasites as hydatid, and *Eustrongylus gigas* in rare instances; or the occurrence of direct injury.

Morbid Anatomy.—When pyelitis, whether acute or chronic, is associated with retention of urine within the renal pelvis, the mucous membrane by degrees assumes a dull white colour, is markedly thickened, and forms pus. The pent-up urine soon becomes alkaline from admixture with pus, urea is converted into carbonate of ammonium, and phosphatic calculous material is often deposited upon the lining membrane of the organ. As the distension of the cavity of the kidney proceeds, the orifices by which the calyces and pelvis communicate often become narrow and even entirely closed, the pyramids, and then the cortex of the kidney, become more and more atrophied, until at length all the glandular tissue is completely removed, and the organ is transformed into a multilocular or many-chambered cyst. Its relations and connexions with the surrounding structures vary. Sometimes it forms adhesions on all sides. Ulceration of the cyst wall, or suppurating tracks burrowing through what remains of the renal substance, may end in fistulous openings, periæphritis, peritonitis, or the discharge of pus and urine by the mouth or rectum, or through some opening on the surface of the body, most frequently in the loin (see "Renal Fistulas").

The fluid contained in the distended kidney is occasionally pus with blood, or pus so concentrated that there is hardly a trace of urine. If it has become changed by decomposition and the development of ammonia, it is more or less thready and glairy; at other times it is a soft mortary material, of a white or buff colour; in other cases it is of the consistence of butter. When a calculus is formed in the kidney, it often assumes a branched form which exactly fits the pelvis and calyces. Sometimes independent calculi occupy the pelvis and calyces. Incomplete and

persisting, or complete but interrupted obstruction to the escape of urine or pus from the kidney pelvis gives rise to the greatest degree of expansion of the organ. When the obstruction is complete and persistent, the parenchyma of the kidney atrophies rapidly, and before the calyces and renal pelvis expand to any great degree. In some cases the kidney becomes completely sacculated, and left without a trace of glandular tissue ; subsequently it shrinks to much below the normal size. Pyonephrosis is sometimes spoken of as being open or closed—"open" when there is an outlet to the bladder for some of the pus ; "closed" when the pus cannot escape at all, or only to the smallest degree, from the renal cavity.

Symptoms.—In the early stages the symptoms are those excited by the cause of obstruction, and in addition those of pyelitis.

If the obstruction be not complete, there will be pus in the urine ; if intermittent, there will be times during which more pus is discharged than at others ; if complete and permanent, there will be an entire absence of pus in the urine. There will be constitutional symptoms of suppuration. When a tumour forms in one or other loin, it possesses the same characters as a hydronephrotic tumour. It is elastic or fluctuating, or nodulated and hard, and bulging the flank as well as occupying more or less of the abdomen. When the tumour is not of great size, there may be a line of resonance above it ; but if it be of considerable dimensions it may have formed adhesions with the under surface of the liver or spleen, and so simulate a tumour or enlargement of one or other of these organs. If very large, the tumour has almost always a more or less nodulated or lobulated outline, and the resonance of the distended colon may be elicited on the outer side ; when this is the case, and fluctuation is also distinct, hydro- or pyo-nephrosis is clearly indicated. The pain experienced depends greatly on the size of the tumour ; in some cases there are paroxysms of great severity. Pressure over the front of the tumour nearly always aggravates pain, or provokes it if it were not present before. Pressure over the flank, in some cases, is not only well borne, but actually gives relief.

When the cause of the obstruction is intermittent in its action, the lumbar tumour will diminish, or may even disappear altogether after the discharge of pus. The urine should be frequently and closely watched, and a record kept of the total quantity passed during each twenty-four hours.

If the ureter be completely blocked, the total quantity of urine excreted, for a short time at least after the occlusion, will be markedly diminished in quantity. If partially blocked the quantity of pus and urine will vary from time to time, even during the same day ; and if the cause of the obstruction shift so that the ureter, from being quite blocked at one period, becomes patent at another, large quantities of purulent bloody urine will be passed during the periods of patency ; the urine in the intervals of occlusion being nearly or quite clear and natural, provided the opposite kidney be healthy.

Diagnosis.—The tumours which may be mistaken for pyonephrosis were thus enumerated by Rayer :—"On the left side of the abdomen, all those which result from morbid enlargement of the spleen ; on the right side the tumours of the liver and gall-bladder ; on either side the various renal tumours of another nature, such as hydronephrosis, haemorrhage into the cavity of the pelvis, cancer of the kidney, tubercle, kidneys containing hydatid cysts ; extrarenal abscess, either idiopathic or consecutive to perforation of the kidney or of the colon or caecum ; abscess arising from caries of the spinal column ; tumours of the suprarenal capsules ; aneurysms of the aorta ; encysted tumours of various characters, hydatid or otherwise ; and lastly, faecal tumours from the accumulation of faecal matter in the colon or caecum."

Pyonephrosis is nearly always preceded and accompanied by febrile symptoms ; the tumour is more or less painful, and the pain is increased by pressure over it, and by movements of the trunk ; and when the ureter is not absolutely occluded, there is the presence in the urine of pus. In hydronephrosis there is an absence of febrile symptoms and of pus in the urine. In perinephric abscess there is even more pain than in pyonephrosis, the course of the fever is more severe and rapid, the fluctuation succeeds to ill-defined hardness about the loin and iliac region and not to a gradually developing circumscribed tumour. In this condition there is extreme tenderness before there is any sign of fluctuation or elasticity ; the thigh is often flexed upon the abdomen, and cannot be extended without much pain ; there is generally redness and oedema of the skin of the loin ; there is no pus in the urine ; and when pus has formed in the circumrenal tissue, fluctuation is more easily made out, and is more superficial than in pyonephrosis.

Inasmuch as nephrotomy is the appropriate treatment for this last condition as well as for hydro- or pyo-nephrosis, the exact differentiation between these conditions is not so important as it would otherwise be ; for when the incision is made the exact state can be ascertained, and the appropriate course of action adopted. It is sometimes impossible to diagnose ascending suppurative pyelonephritis with general enlargement of the kidney, from pyonephrosis. Tumour, high fever, rigors, and pus in the urine are common to both diseases.

Prognosis.—In cases of cancer of the pelvic organs, of suppuration in or around the vesical walls, or of impaction of a calculus on one side with disease of the opposite kidney, the fatal prognosis is determined by the nature of the cause. When pyonephrosis of one side only is produced in persons with previously healthy kidneys, by some cause which occludes the ureter and does not interfere with the opposite kidney, the prognosis, as regards life at least, and generally as regards the kidney also, is good if early relief to the pent-up urine and pus be given.

Treatment, in the early stages, consists in the removal, if possible, of the cause of obstruction and distension. If the cause be a removable or a remediable one, such as stricture of the urethra, or prostatic enlargement, attention must be addressed to that. Tumours of the ovary,

uterus, and of the bladder should be removed when possible. If a calculus is felt in the vesical orifice of the ureter, it should be extracted ; and in certain cases in which the cause of the obstruction is a calculus impacted in the ureter, too high to be felt from the bladder and too low to be reached through the kidney, ureterotomy is required. When the cause of the obstruction has not long existed, and is probably a small calculus or a plug of mucus, pus, blood, or false membrane in the ureter, it may be displaced by freely drinking hot liquids, such as weak tea. But such tentative and expectant treatment ought not to be prolonged.

Palliative treatment of the tumour is permissible, for a time at least, where obstruction is not complete and the pus and urine can escape by the ureter. In most instances, however, the proper treatment is nephrotomy, palliatives being useless and delay dangerous. The circumstances which indicate nephrotomy are : constant pain, increasing size of the tumour, continued fever, severe gastric and intestinal disturbance from irritation or direct pressure of the tumour ; inflammation of the surrounding tissues or adhesion of them to the tumour ; and a threatening of rupture or ulceration of the tumour. Secondary or, in some cases, even primary nephrectomy may be demanded. Plastic operations on the renal pelvis and ureter are much less favourable where there is suppuration than in cases of simple hydronephrosis.

C. Haematonephrosis and Uro-haematonephrosis.—This, the third variety of nephrectasis or renal distension, is rare, much rarer than either of the other two forms, namely, hydronephrosis and pyonephrosis.

Etiology.—Injury, renal calculus, renal new growth within the pelvis of the organ, mobility of kidney, continued fever, purpura, and many other conditions lead to it. Hydronephrosis may become uro-haemato-nephrosis by the giving way of a vessel on the inner wall of the sac. This is more likely to occur in the intermittent form of hydro-nephrosis, and to follow the sudden emptying of the renal cavity. The haematonephrosis due to injury may be slowly produced if the blood escapes from a small vessel, or very rapidly if its source is a branch of the renal artery or a ruptured renal aneurysm.

Morbid Anatomy.—This varies greatly in different cases, as it does in hydro- and pyo-nephrosis. The contents of the sac may be thick and inspissated, or thin and watery ; pure blood, or black and like treacle ; or decolorised and in concentric layers. If the case is of long standing the blood may be consolidated into a hard, nearly decolorised, mass.

Symptoms.—These may be slight and of slow onset, or severe and very rapid in their progress, depending on the nature of the cause and the source of the bleeding. Haematuria, pain, and tumour are the three classical symptoms ; but any or all may be slight, considerable, or absent.

Prognosis.—This depends on the cause of the haemorrhage, and on the condition of the renal pelvis and ureter. If the channel to the bladder remains patent, prolonged or frequently recurring haematuria may

destroy life. When the blood comes from a large branch of the renal artery, the kidney or its pelvis is apt to give way, and great extravasation into the perinephric tissue to follow, and death to ensue from loss of blood or the pressure effects of the tumour ; or infective changes may occur in the blood mass. Even if life is not threatened, the prospect of saving the kidney is very poor.

Treatment.—If the patient's condition is unfavourable to an operation, and if life, from loss of blood, is not immediately threatened, it may be the surgeon's duty to stand by and watch, well knowing, however, that the kidney will be destroyed. But if an operation is not contra-indicated, nephrotomy and the control of the bleeding point, or nephrectomy, or nephro-ureterectomy must be performed.

Subcapsular Haemorrhage.—The comparatively rare condition brought about by haemorrhage beneath the capsule of the kidney is liable to be mistaken for tumour or other renal enlargement, or for calculous disease of the kidney. Subcapsular haemorrhage may result either from direct trauma or indirect strain ; the quantity of blood effused varies from a few drams to a pint or more. The symptoms produced are local pain, tenderness or discomfort, and undue frequency of micturition. They are, in fact, very similar to those resulting from the presence of a renal calculus, with or without the haematuria ; and in those cases in which the blood effusion is large it is not at all unlikely, by its bulk and renal contour together with the hardness and nodulation which result from coagulation, to simulate a renal tumour very closely.

The subsequent effect of organisation and contraction of the clot is to compress the organ and seriously to impair its function, so that early relief by operation is of importance ; and the difficulty of distinguishing between it and calculous or other forms of renal enlargement or nephrectasis, except by exploration, becomes of less moment. The history of the affection may be a guide in some instances, the symptoms occurring suddenly, and dating from a blow or wrench. Such an accident, however, so readily calls attention in the first instance to a tumour, or causes sudden pain and enlargement by haemorrhage from a previously existing new growth, that too much reliance must not be placed upon it.

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XII. TUBERCULOSIS OF THE KIDNEY occurs in two forms, the miliary and the caseous. Miliary tuberculosis more frequently affects the kidneys of children under ten years of age, whereas the caseous form is generally met with in young and middle adult life, but occurs also in persons past middle age. The earliest stage of all forms of tuberculous disease is the miliary, but it is the aggregation of these miliary tubercles into grey and yellow nodules and then into masses, and the subsequent degenerative changes in the masses, which give rise to symptoms suggesting and requiring treatment directed to the organ affected. It will not be necessary to consider the miliary affection further here.

Etiology.—The tubercle bacillus which is the cause of the disease may reach the kidney either through the circulation or the lymphatics, or by way of the ureter, ascending from the urethra, seminal vesicles, prostate, or bladder; very rarely it reaches the kidney through its capsule, by extension from some other organ or cavity, as in a case recorded by Dr. Newman, in which a tuberculous empyema perforated the diaphragm and invaded the kidney. Advanced tuberculosis of the adrenals spreads to the perinephric tissue, but does not penetrate the renal capsule.

In the majority of cases the disease first attacks one kidney only, and when the other is affected it is at a much later date. The records of autopsies shew that the caseous form of renal tuberculosis is found to be bilateral as often as, if not somewhat more often than, unilateral, but these records have reference to periods when the disease has lasted a long time, and do not tally with the clinical experience of the disease in its earlier stages. It attacks males somewhat more frequently than females, and is more often associated in them with tuberculosis of one or more of the other genito-urinary organs than is the case in the female.

Pathological Anatomy.—The kidney may be affected without infection of either its ureter or the bladder. The cortical and the pyramidal areas are about equally often the first to be attacked. When the disease commences in the kidney, it may spread in a descending manner along the ureter and invade the bladder. Conversely the ureter and then the kidney may be secondarily diseased by an ascending tuberculous invasion from the bladder; and when the latter is the mode of origin of the renal affection, the morbid process spreads from the apices of the pyramids into the rest of the parenchyma. The kidney may be reached by the tubercle bacilli travelling along the lymphatics from the bladder, without infection of the intervening ureter. Following the course of the blood-vessels the tubercle bacilli may reach those of the Malpighian tufts, and there become the starting-points of the pathological changes in the organ. Experimental pathology has also shewn that dead micro-organisms, as well as the living bacilli, may set up the early cellular proliferation of the

tuberculous process. It is not difficult, generally, to say what has been the mode of infection. When by the blood, miliary tubercles are found in the cortical substance, the caseous nodules are older and wider about the bases of the pyramids than near their apices ; and if they have broken down and opened into the calyces, the openings of the vomicae are small, even though the parenchyma may be almost entirely destroyed. Moreover, there may be little or no extension of the morbid process into the renal pelvis or the ureter. When the disease is of the ascending type the ureter and renal pelvis are at first the seats of small submucous plaques, and become indurated, thickened, and perhaps ulcerated, with a quantity of cheesy material in their walls or in their lumina, which may ultimately completely occlude them and lead to hydro- or hydro-pyonephrosis, or otherwise to complete destruction of the kidney. The calyces share in the changes in the ureter and renal pelvis ; the connective tissue and urinary tubules become invaded from below upwards ; the vessels become obliterated, minute haemorrhages occur into the tissue, and the destructive process spreads from apices to bases of the pyramids till large vomicae are formed, which communicate with the renal pelvis by wide openings. The caseous masses may also, though more rarely, break through the fibrous capsule of the kidney, and set up tuberculous perinephritis, or invade the contiguous surface of the liver or spleen. If the tuberculous foci are invaded by pyogenetic organisms, abscesses result, and the clinical course of the tubercle is rendered more acute, and the lesions caused by the pyogenetic infection are more serious and persistent. When the ureter is occluded in the course of the ascending invasion, or by the impaction of caseous material or lime salts which have descended from the kidney, tuberculous pyonephrosis may result. The body of the kidney is often enlarged and lobulated by numerous cheesy nodules in the cortex, which, on section, are found to be more or less completely circumscribed and in different stages of softening. The renal parenchyma between the tuberculous masses may be quite healthy, or dense and tough from interstitial sclerosis, or its tubules may be dilated and stuffed with degenerated epithelial cells. Thus, if pyogenetic infection has occurred, the whole organ may be converted into a series of abscesses, or converted into one huge abscess by the gradual softening and destruction of the intervening tissues, with caseous and puriform debris for contents.

In some cases in which the ureter is obstructed the kidney is converted into a large, tightly distended, and more or less lobulated sac, filled with a thick white putty substance which has taken the place of every trace of renal substance. In other cases the kidney becomes a mere shrunken putty-like mass, in which abundance of cholesterol or calcareous nodules are formed in the lobulated spaces. In other cases the disease may take the form of an infiltrating intertubular tuberculous fibrosis. In cases of renal tuberculosis of long standing the perinephric tissue is apt to become the seat of chronic inflammation, either sclerosing, or, what is very common, of the fibro-lipomatous variety. Very firm

adhesions unite the kidney and renal pelvis with the perinephric tissues, the vena cava, the aorta, and other structures. The lymphatic glands at the hilum of the kidney may also be tuberculous, and be firmly adherent to the surrounding structures.

The operating surgeon should remember that a kidney may be the seat of extensive discrete miliary tubercle, without there being any evidence of tuberculous disease on the surface of the organ. Tuberculosis of the kidney is sometimes associated with carcinoma of the genito-urinary organs, such as the kidney or bladder.

The malarial parasite gives rise to foci the size of a pin's head in the cellular tissue around the renal blood-vessels, which they obliterate. They are formed of embryonic cells and leucocytes, and may be mistaken for tubercle, but they never caseate or suppurate. They often cause haematuria.

Symptoms.—There may be enlargement of the kidney from tuberculous cheesy masses, and yet an entire absence of symptoms. Persons who have never had any localised symptoms, or change in their urine, or any undue frequency of micturition have, after death, been found to shew tuberculous masses in both their kidneys. The symptoms in the early stage vary according to the manner in which the kidney is invaded by the tubercle bacilli. When the infection is by the blood, there may be neither local nor urinary symptoms until a tumour is formed or the renal calyces have become invaded. In the chronic infiltrating or caseating forms the symptoms are slow in developing, and may never be severe unless suppuration supervenes.

When the kidney is invaded by way of the ureter, pain, haematuria, urinary changes, and tumour are prone to appear at an early stage. The various symptoms to which renal tuberculosis may give rise are the following: lumbar pain, dysuria, polyuria, frequent micturition by night and by day, haematuria and pyuria in acid urine, the presence of tubercle bacilli in the urine, pallor, loss of flesh, night-sweats, some elevation of temperature especially in the evening, reaction to the injection of tuberculin, and a low opsonic index.

Pain in the loin increases as the disease advances; slight pain has often existed for many months, sometimes for a year or two, before the patient seeks medical advice; it is often referred to the loin of the affected side, sometimes to the pelvis or groin, or along the course of the ureter. Colic is sometimes the result of caseous particles passing down the ureter. There is often tenderness on palpation over the affected organ.

Tumour.—Some increase in the volume of the kidney is exceedingly common; and in a large number of cases, though there is no nephrectasis, the tuberculous kidney in the middle and advanced stages gives rise to a swelling which can be easily detected by the movement known as *ballottement*. A tumour may form insidiously and be the only symptom. Occasionally changes in the surrounding perinephric tissue give the impression that the kidney is enlarged when it is not really so. The

outline of an enlarged tuberculous kidney may be uniform, or lobulated owing to the presence of several masses, or irregular from one large mass or a tuberculous abscess expanding one part only of the organ. If it be painful and tender the pain may be either local, or radiate in various directions towards the loin, abdomen, or groin.

Urine.—Polyuria is a frequent and early symptom; it shews itself sometimes in fits and starts, and it is often associated with dysuria. It may be the only symptom in the early stage of the disease, and it should always arouse the suspicion of incipient renal tuberculosis when it occurs in a person of weakly constitution, especially if he is losing flesh. In the later stages of the disease the quantity of urine passed is frequently below the normal, and may contain debris of renal tissue and minute particles of cheesy tissue, besides varying quantities of blood or pus or both. Renal epithelial cells and hyaline and granular casts point to nephritis, which not very rarely coexists with renal tuberculosis.

Pyuria.—In most cases there comes a period when pus is present, or at any rate leucocytes resembling pus. The urine containing the pus is nearly always acid, and the pus is frequently sterile; it has often a peculiar dirty-grey colour, and does not give the urine the foul smell so generally noticed in cystitis. Mixed with the pus may be small mortary phosphatic particles, in some of which bacilli may be found.

Haematuria is not unfrequently the earliest symptom, and in most cases traces of blood, often, however, only microscopic, are to be found in the urine from time to time. It is intimately mixed throughout with the urine; if intermittent, it is quite independent of either rest or exercise. It is often present with pyuria. It has, in exceptional instances, been so excessive and persistent as to endanger life. It should, however, be remembered that haematuria, as a rule, is neither constant nor profuse in renal tuberculosis.

Tubercle Bacilli.—Their presence in the urine is of the highest importance; not so their absence. Even with reference to their presence, it must not be forgotten that they have been proved to pass through the kidneys without infecting those organs. This may give rise to great difficulty in diagnosis. It did so in a very notable manner in the case of a gentleman, aged sixty-four, upon whom I performed nephrectomy in Bombay in December 1904. There was a large tumour in the right renal region, attended with very great suffering, and tubercle bacilli were found in the urine; but the kidney was the seat of calculous pyonephrosis with large and multiple calculi, and not a trace of tuberculosis was discoverable on most careful examination by the same pathologists who found the bacilli in the urine on repeated occasions. In this patient there was a mass of enlarged glands of very long standing above the left clavicle, and he died subsequently of tuberculous pleurisy with effusion. Tubercle bacilli are often absent from the urine in cases of primary renal tuberculosis, and in cases in which the ureter is blocked the most patient search is often needed to discover them, and they may be found in one only out of many slides. The best means of

ascertaining their presence is by inoculating several guinea-pigs with the urine. It is useless to inoculate only one or even two. It is hardly requisite to refer to the necessity of excluding the possibility of mistaking the smegma bacillus for the tubercle bacillus.

Frequent Micturition and Dysuria.—Vesical irritation and painful micturition are not at all unusual, and in some cases have been the most pronounced and very early and very distressing symptoms, although the bladder and lower urogenital organs are quite free of disease.

The general symptoms have been already referred to, and need hardly be mentioned here at greater length. When suppuration supervenes upon renal tuberculosis, the greater part of the general symptoms may be due to the pyogenetic and not to the tuberculous infection.

The Opsonic Index.—Investigation by this means is not likely to be overlooked at the present period (30, 35).

Diagnosis.—The early diagnosis of renal tuberculosis is of very great importance because of the adoption of suitable expectant treatment, with or without the employment of bacterial vaccines. By attention to the symptoms which have just been described, there is little excuse for mistaking renal tuberculosis for any other disease, if most of those symptoms are present. The possibilities of error have, however, been mentioned in the description of the symptoms. The discovery of tuberculous lesions in other organs of the same person will generally assist the diagnosis, but may in rare cases confound it by causing the presence of tubercle bacilli in the urine, as in the case referred to above.

Renal calculus is the affection for which formerly renal tuberculosis was most often mistaken, but at the present day the perfection to which skigraphy has been brought obviates this error in diagnosis almost entirely; there is, however, the exception that a caseous mass undergoing calcareous change has more than once given rise to the expectation of finding a renal calculus where there was none. The general symptoms and the characters of the haematuria—which in renal calculous affections is not only intermittent but is subdued by rest and induced by exercise—and the pyuria will in most instances distinguish the two diseases.

New growths of the kidney are also sometimes mistaken for renal tuberculosis, and I have met with one instance in which, even after the removal of the kidney containing the growth, the naked-eye appearances resembled a tuberculous caseous mass, the nature of the disease being only cleared up on microscopic examination.

As to which Kidney is Affected.—There will very rarely be a doubt as to which kidney is the seat of the caseous form of tuberculosis suitable for operative treatment. The cystoscope and the ureteral catheter lead to many fallacies, and should be employed with the greatest caution in tuberculosis of the genito-urinary organs; and if the bladder itself is the seat of the disease the ureters in my opinion ought on no account to be catheterised. In view of surgical treatment it is of the utmost importance to ascertain whether the opposite kidney is healthy or not, but the

absence of tuberculosis cannot with safety be inferred from the absence of tubercle bacilli or other abnormal constituents in the urine, whether obtained by the segregator or the ureteral catheter. When the kidney known to be affected is from time to time closed by ureteral obstruction, the urine from the opposite kidney may thus be ascertained to be normal ; and although this may afford *prima facie* evidence of the functional value of the organ, it gives no absolute indication of its freedom from tuberculous disease.

Prognosis.—Unless the disease is strictly localised and detected early enough to be cured by expectant treatment, or radically removed by operation, the prognosis is most unfavourable. Undoubtedly many cases are known to have recovered spontaneously, but this happy termination can never be anticipated. The disease is prone to progress by fits and starts—periods of activity being succeeded by long intervals of comparative or complete quiescence, so that the hope is raised for a time that the case is cured. It is by no means unusual for the disease to extend over four or five years, or even many more ; its duration, in fact, varies much from a few months to several years. Its course is hastened by the supervention of secondary pyrogenetic infection ; and occasionally, though very rarely, by profuse haematuria. The complication of suppurative pyelonephritis is one of the gravest import. When the disease tends to spontaneous recovery, it is by cretification of the caseous material, or by atrophy of the entire kidney owing to complete occlusion of the ureter. The causes of death are asthenia, septicaemia, anuria, and uraemia. The prognosis after operative treatment has very greatly improved during the last ten or fifteen years.

Treatment.—The methods of treatment are (1) the expectant ; (2) the operative ; and (3) the injection of bacterial vaccines. The expectant treatment, or the general, dietetic, tonic, open air, and rest treatment, may or may not be combined with the employment of bacterial vaccines. The injection of bacterial vaccines may or may not be combined with the expectant method, though most commonly it is. These methods are employed in renal tuberculosis in the same manner as for tuberculosis of other organs, and therefore it would be superfluous to enter into details about them in this section. I will only remark that the claims which have been advanced in favour of the treatment by bacterial vaccines, guided by the opsonic index, in tuberculous diseases of the genito-urinary organs, including the kidney, have not been as yet conclusively substantiated ; still less has it been satisfactorily established that the new tuberculin treatment is destined to supplant all other methods of treatment hitherto employed. From what we learn at present there seems to be no finality as to its duration. There are many diseased conditions under which it ought to have a full and fair trial. But in spite of my having, I hope, an open mind as to its future and, possibly, its increased value, I do not think that it has yet proved its claim to modify, still less to take the place of operative treatment as practised at the present time.

The rules which should be observed as to operating may be briefly summarised as follows:—(1) That operative treatment should not be resorted to in the early stages until full and fair expectant treatment has been tried; (2) that operative treatment, even in the middle and later stages of the disease, should not be employed on a tuberculous kidney that is not causing constant or worrying pain, or symptoms interfering with the patient's ordinary mode of life or general fair state of health, nor when the disease is known to be bilateral, nor when other organs are affected, except as a means of giving temporary relief; (3) that when operation is performed partial nephrectomy should be preferred to total nephrectomy, if the disease is clearly limited to one pole of the kidney or to well-circumscribed cysts or foci; (4) that total nephrectomy is to be preferred where the whole or greater part of the kidney is involved, or the disease, even though localised, is, as judged by the temperature and other general symptoms, deemed to be in a very active state. Under these conditions partial nephrectomy is likely to be followed by very rapidly spreading disease in the rest of the kidney and in the perinephric tissue; (5) that nephro-ureterectomy is indicated when the ureter as well as the kidney is markedly diseased; (6) that nephrotomy with a view to subsequent nephrectomy should be avoided when possible, because of the danger of the perinephric tissue becoming infected by the discharges from the kidney.

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XIII. ACTINOMYCOSIS OF THE KIDNEY.—*Streptothrix* infection of the kidney is perhaps not quite so rare as has been supposed. It has scarcely ever been mentioned in standard works on either medicine or surgery, and this is probably due to the close similarity which renal actinomycosis presents clinically and microscopically to tuberculous disease of the kidney. It is only on careful examination after removal from the body that the small granules contained in the pus have proved to be masses of a *streptothrix* parasite. Dr. Acland in a collection of 109 cases of actinomycosis recorded in Great Britain found 5 renal cases (Vol. II. Part I. p. 332), von Bergmann in his recent work on surgery referred to it, and Mr. Kellock in 1905 published an illustrative case, the pus from which was examined and the organism it contained isolated in pure culture by Mr. Foulerton (*vide* Vol. II. Part I. p. 310). The patient, a married woman thirty-one years of age, complained of pain, tenderness, and swelling in the right renal region. She had shivering fits, and had noticed that the urine sometimes was of a grey colour, and deposited a sediment on standing. When she came under observation the tumour extended from the lumbar region into the umbilical, hypochondriac, and iliac regions, and she had a pulse-rate of 120, and a temperature of 102° F., which rose on occasion to 104° F. The urine was acid, of high specific gravity, less than half the normal in quantity, and at one time was free of, and at another contained, blood and pus. In the course of the operation of nephrectomy the tumour was tapped to reduce its size previous to delivery through the lumbar incision; it was not very adherent to the surrounding structures, and, except below, was fairly easily freed. In this respect it was unlike the generality of tuberculous enlargements of the kidney of similar size. It measured 7½ inches in length, and was largely lobulated on its surface; and on section it was seen to be made up of spacious cavities containing greenish-looking and offensive-smelling pus. Very little renal substance separated these cavities from the surface of the organ; and the cavities themselves were

lined with what at the time was regarded as "tuberculous-looking" material. Some of them communicated with the renal cavity and also with the ureter, which contained the same sort of pus. The ureter was affected below the level at which it could be removed. The patient made a good recovery from the operation, but the disease quickly recurred in situ; and within nine months from the date of operation there was a suspicion that the lung had become secondarily affected. Treatment with large doses of potassium iodide was continued for a long time, and she was seen by Mr. Kellock in March 1908 apparently quite well. (*Vide* also articles on "Streptothrix Infections," and "Actinomycosis," in Vol. II. Part II.)

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XIV. SYPHILITIC AFFECTIONS OF THE KIDNEY occur during the early and secondary, as well as in the late stages of acquired syphilis; they are met with also in the congenital form of the disease.

Pathology and Symptoms.—At the commencement of and during the secondary period of syphilis, it is not uncommon to find some albumin in the urine, and more rarely a definite nephritis exists. The albuminuria is generally transient, and appears about the same time as the secondary rash; it is not usually accompanied by any definite symptoms, and is doubtless very often overlooked. Less commonly a definite acute nephritis occurs, which runs the clinical course of acute nephritis when due to other causes, and terminates in resolution, or in the chronic tubular nephritis resulting in the large white kidney. Microscopically the secreting structures are the parts chiefly affected, and in some instances the appearances closely resemble those found in the kidneys in scarlet fever. The symptoms of these acute cases have nothing special in their character. They either run an acute course terminating in resolution or uraemia; or they are intermittent with well-defined intervals, the albuminuria continuing long after all other symptoms have quite disappeared. Until within the last few years the albuminuria and the acute forms of nephritis which occur during the secondary stage of syphilis were thought by many to be the effects of mercurial treatment. It is probable, however, that the careful and moderate use of mercury does not cause albuminuria; and it is certain, on the other hand, that many patients derive direct benefit from ordinary antisyphilitic treatment. During the later stages of syphilis, affections of the kidney are more common than in the earlier stages. The interstitial and the amyloid forms are the most frequent, but the acute and chronic parenchymatous and the mixed varieties also occur in the later periods of the disease. The kidneys in which the interstitial changes are present are usually much diminished in size and often irregular in shape, and scarred on

their surfaces. The interstitial tissue is greatly increased, the walls of the arterioles thickened, the tubules frequently obliterated, partly by compression and partly by their own epithelial cells, which are undergoing fatty and granular degeneration, and the renal capsule is often so greatly thickened and nodular as to give rise to the impression that the kidney proper is enlarged, though it is not found to be so when the capsule is removed. Gummas are rare, and occur usually as small deposits from the size of a pin's head upwards, in either the cortex or the pyramids, but several cases in which a gumma as large as a potato, or even large enough to take the place of the whole of the cortical and pyramidal areas, have been recorded. Gummas may give rise to no symptoms whatever during life, beyond the presence of a little albumin in the urine, which, though less frequently, may also contain renal epithelium, pus, and a few hyaline casts. When of large size they are liable to be mistaken for malignant new growths, or for tuberculous masses in the kidney, and in several cases nephrectomy has been performed under this misapprehension. In a case under my care of a man, sixty-four years of age, with carcinoma of the bladder, both kidneys were very extensively changed by multiple small gummas and marked lardaceous change in all the renal vessels. The symptoms, which terminated in the death of the patient, were violent delirium, gradually increasing suppression of urine, dry skin with entire absence of sweating, diarrhoea, no lumbar pain, and great increase in arterial blood-pressure, which gradually lessened during the last few days before death.

Diagnosis.—The nephritis of early syphilis, which is chiefly of the tubular or parenchymatous form, has nothing special about it either in onset, course, or post-mortem appearances. The diagnosis rests only on the relation between syphilis and the nephritis, as revealed by the history of the case. Great care should be taken to exclude all other possible causes of nephritis before its direct dependence upon syphilis is admitted.

In nephritis of late syphilis, which generally is of the chronic interstitial, more rarely of the gummatous type, the diagnosis will depend on a definite history of syphilis, and the presence of tertiary evidences elsewhere,—other causes being excluded.

Prognosis.—Improvement under specific treatment may serve to distinguish a large gummatous kidney from a renal new growth. Gummas occasionally disappear, leaving behind them traces in the form of scars and considerable depressions on and near the surface. The prognosis in syphilitic nephritis is difficult, but a large amount of albumin, the presence of epithelial and fatty casts in the urine, and the onset of respiratory or other complications are very unfavourable. (*Vide* also p. 605.)

Treatment.—The treatment of syphilitic nephritis should be conducted on the same general lines as for nephritis due to other causes, except that mercury is not contra-indicated, provided its effects are carefully watched. Often the renal symptoms subside rapidly under its influence.

In the later stages of syphilis, potassium iodide should be given; but in most of these cases the connective-tissue changes are so far advanced before symptoms arise that but little benefit can be expected from medicinal treatment.

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XV. RENAL CALCULUS.—If the crystalloid substances, normally in solution in the urine, are deposited in excess, become cemented together around a fragment of organic matter such as mucus or blood-clot, and are subsequently added to by fresh depositions from the urine, a calculus is constructed which may either be discharged with the urine, causing more or less renal colic in its transit along the ureter, or may remain behind in one of the tubules, or in one of the calyces, or in the pelvis of the kidney, there to grow by fresh accretions, until it gives rise to a small abscess in the renal parenchyma or attains a size altogether in excess of anything which can pass along the ureter. The formation of a stone in the kidney is the result of some defect in general metabolism, and is occasionally preceded by a deposit of crystals, granules, or gravelly deposit which escapes with the urine.

The tendency (hereditary in many cases) shews itself about equally in the two sexes, in childhood and after middle life. It is aggravated by a sedentary life, by insufficient fluid, and by an excess of nitrogenous or saccharine food, and possibly of the salts of lime. Renal calculus occurs with peculiar frequency in certain localities, such as in Scotland, Norfolk, Moscow, and the Delta of the Nile.

The deposition of solid matter depends, in the first instance, either upon the presence of an abnormal and insoluble product of tissue change, or of a normal product present in such excess as to be insoluble in the urine, or precipitated on account of alteration in the reaction of the fluid, which may be alkaline or excessively acid. In a great many instances the deposit is found to collect around a foreign body or a small nucleus of organic matter, such as a mass of epithelial cells, a blood-clot, or a parasite. There must be present a "colloid" of some sort to hold together the crystals or salts in the urine (*vide Vol. III. p. 263.*).

The most common form of renal calculus in the adult is the uric acid, the next most common the oxalate of lime; but carbonate of lime, phosphate of lime, a mixture of phosphate and the ammonio-magnesian phosphate (the fusible calculus), cystine, xanthine, urate of ammonium, or the mixed urates, are occasionally, though rarely, found as the nuclei or chief constituents of renal stones. Calculi composed of uric acid, oxalate of lime, and phosphates in alternating layers are not uncommon. Renal calculi are formed at all periods of life.

The nucleus in the case of an infant is usually ammonium urate; that in a person of about fifteen or sixteen years of age consists of uric acid, whilst after the fortieth year oxalate of lime more frequently constitutes the nucleus. One or many calculi may be formed in the same kidney; when composed of lime oxalate the calculus is usually but by no means invariably single.

A renal calculus may be a small, round, smooth, or very rough and tuberculated body, or a large, smooth or rough, branched mass filling all the pelvis and calyces. A stone as large as a marble, sharply mammillated on its surface, may remain confined to one of the calyces for years without giving rise to more change than induration of the whole organ due to slight or chronic interstitial inflammation. On the other hand, quite a minute stone in the tubular structure of the kidney, not much or any larger than a mustard seed or grape seed, will excite congestion, and even acute inflammation and abscess. I have known a small rough calculus, not larger than a very large grape-stone, impacted in the upper part of the ureter nearly cause death from haemorrhage. It was so firmly impacted in the mucous membrane that it had literally to be dug out.

Renal calculi do not attain to such large dimensions, as a rule, as those which occur in the bladder. They differ much in size as well as in shape and colour, varying from that of a hemp-seed to that of a small walnut; but in exceptional cases they may be very much larger. The large branched phosphatic calculi have been known to weigh as much as 1500 grains. The largest stone I have taken from the kidney during life weighed 10 oz. They are usually rounded or oval, unless moulded to the pelvis or calyces, when they may be irregular or branched and coral-like. The surface is usually rough or mammillated. The colour differs with the constitution of the calculus, and may vary in different layers. It is mostly purplish-brown in oxalate of lime, reddish-yellow in uric acid, and greyish-white in phosphatic calculi. Exceptional specimens being yellow, pink, green, or blue. Cystine calculi are fawn-coloured, soft and greasy to the feel, are often multiple and prone to occur in several members of the same family. Xanthine calculi are rare; they are formed, however, under the same clinical conditions as uric acid.

The liability of the kidney to calculus is equal on the two sides, and in about 15 per cent of the cases both organs are affected at once.

Pathology.—The presence of a calculus in the kidney does not necessarily provoke immediate and extensive changes in the organ. It may exist for some time at least without even exciting recognisable

symptoms, especially when it is fixed in such a position as not to interfere with the function of the gland.

Atrophy of the kidney is found in some cases, chiefly after death, in association with calculus; the kidney being reduced to a mere fibrous capsule around the stone. It would appear that in these cases the calculus has been loose, or so situated as to obstruct the ureter or renal pelvis, whence followed more or less distension of the kidney, absorption of the secreting substance, and subsequent contraction of the sac.

In other cases in which the calculus has caused obstruction of the renal pelvis and ureter, there ensues great distension of the kidney, beginning in the pelvis and extending to the calyces and parenchyma. Dilatation of the renal pelvis is frequently associated with interstitial oedema, and dilatation and contortion of the tubules.

The glomeruli atrophy, the cells of the connective tissue proliferate, and the vessels become thickened. At the same time both the fibrous and mucous layers of the pelvis are much thickened; and it depends on the ratio between secretion with obstruction on the one hand and sclerosis on the other, whether the kidney becomes distended into hydronephrosis or ends in contraction and atrophy. The introduction of organisms determines suppurative nephritis, pyonephrosis, or even perinephritis; and, by inducing alkaline decomposition of the urine and secondary deposit of phosphatic salts, may lead to a very rapid increase in the size of the calculus.

Symptoms.—A small stone may form, travel down the ureter, and escape without giving rise to any trouble; and a stone of moderate or even large size may exist for years without causing any recognisable symptom. As a rule, however, there is at some time albumin, blood, or pus mixed with the urine, and some lumbar pain or aching. The pain may be worse at night, but is especially excited by jolting or shaking of the body, and when long continued may lead to lateral flexion of the thorax from muscular spasm. The importance of pain as a symptom of renal calculus depends on its position, persistence, and direction of radiation, together with the accompanying phenomena. In addition there may be pain referred to the opposite kidney or ureter, or to the bladder, with painful and frequent micturition, and at times with some pain in and retraction of the testicle. If the stone have existed some time, pus, mucus, or albumin will be found daily in the urine in a minute, moderate, or considerable quantity. As soon as a stone enters the ureter, or is being propelled along it, renal colic very generally sets in, the attack coming on suddenly, lasting a few hours, or two or three days, and suddenly subsiding, to recur at some future period if the stone, instead of escaping at the lower end of the ureter, is simply displaced from the upper orifice into some less important point in the renal pelvis. Recurring attacks of colic arise also from fresh formation of renal calculi. The paroxysmal pain shoots down the course of the branches of the lumbar plexus, and is felt in the bladder, groin, or thigh, if not in all these

parts ; and is intensified by the spasmodic contractions of the ureter. Collapse and faintness are not uncommon ; the bladder is irritable, and the urine blood-stained and loaded with urates. The attack is often ushered in with a rigor, and generally accompanied by vomiting and profuse perspiration.

When the patient is very thin, and the stone large, it can be sometimes detected on palpation of the loin. I have felt many thus in the living subject. The haematuria is not often profuse or constant, and usually subsides with complete rest in bed ; it is not proportionate to the size, number, or chemical nature of the stones, though it may be remembered that oxalate calculi have the roughest and therefore most irritating surface. When several stones are present, crepitus may be obtained. Microscopic examination of the urinary deposit may disclose casts of the urinary tubules composed of blood-corpuscles, or crystalline masses which have become detached from the surface of the calculus.

Movements such as those caused by carriage exercise, running, or walking are not in all cases needed to cause exacerbation of the lumbar pain ; on merely turning in bed, or even when lying asleep, the patient may be aroused by a sudden agonising seizure.

Apart from the attacks of renal colic, lumbar and renal pain is a very common symptom of stone in the kidney. Owing to the wide nerve-connexions of the kidney, the pain of renal calculus is often transferred to a distance, for instance, to the testicles along the spermatic plexus and the genito-crural nerve ; to the upper part of the thigh by the same nerve, to the leg and inside of the foot by the anterior crural nerve. Paroxysmal lumbar and sciatic pains, accompanied or not by retching, are by no means rare. Sometimes the sciatica is severe enough to keep the sufferer within doors for weeks or months ; and though the pain will be on the side of the calculous kidney, there may be nothing to indicate the cause of it. In all such cases it is prudent to institute a careful examination of the urine for blood, albumin, or crystals, and carefully to review the clinical history, especially as to any past attacks of haematuria.

At the same time uric acid in excess and oxalic acid in the urine are often attended by haematuria, crystals in the urine, and wandering, transferred, and paroxysmal pains in the back, thigh, calf of leg, and sole of foot. Prout states, and Dickinson agrees with him, that uric acid calculus produces the least pain, and that of a dull oppressive character, with a sense of weight ; oxalate of lime produces an acute pain referred to a particular spot, as well as shooting to the ureter, shoulder, and epigastrium ; and phosphates give rise to great and unremitting pain, attended, however, with exacerbations.

Another symptom which results from transference of nerve influence has reference to the stomach : nausea, vomiting, and dyspepsia are very common, not only at the times of actual colic, but also during the periods of less acute suffering. These symptoms are explained through the connexion of the pneumogastric with the renal plexus. The retraction of

the testicle, the irritability of the bladder (which in some cases is the most pronounced and a very distressing symptom), and the pain referred to the thorax sometimes thought to be due to pleurisy, are all explained in the same manner as the gastric disturbance and the pains in the lower limb; namely, by transference of nerve influence.

As is the pain, so the other common symptoms of renal calculus are largely due to the actual contact of the stone with the mucous membrane of the kidney or ureter. These other symptoms are haematuria, pus in the urine, and the occasional sense of fulness or puffiness caused by the mechanical obstruction to the outflow of urine. Pus is a consequence of inflammation of the mucous membrane of the pelvis and calyces of the kidney. Sometimes, as the first sign of pyelitis, before pus corpuscles are seen, the microscope reveals granular corpuscles and epithelial cells or scales, entangled in thick threads of mucus, as well as a few blood-corpuscles. Mucus occurs more frequently when the calculus is of oxalate of lime. The pus of pyelitis occurs in acid urine, is not stringy, and separates readily from the urine on standing. The urine is commonly not offensive.

Tenderness over the affected kidney will often be brought out by pressing on the loin or over the front surface of the organ. The occasionally peculiar attitude and gait of a patient with a renal calculus are due to an effort to relax all pressure on the kidney as much as possible. Thus, as in perinephric abscess, hydronephrosis, and other renal affections, lateral inclination of the trunk and flexion of the thigh are present in some persons.

Among the serious complications of renal calculus may be mentioned renal colic, suppression of urine from obstruction of the ureter, hydro- and pyo-nephrosis and pyelonephritis.

Diagnosis.—Probably the greatest difficulty in diagnosis is between early tuberculosis of the kidney and renal calculus. When frequency of micturition and slightly purulent urine are met with in a person of tuberculous diathesis, and are unaccompanied by a history of haematuria, the nature of the disease is indicated; but when these symptoms are associated with a history of haematuria and sharp lumbar or testicular pain in an otherwise healthy-looking person, the diagnosis of calculus is made still more probable.

Lumbar pain may be due to neuralgia of the parietes or of the kidney itself; but there is not the local tenderness on examination which is met with in renal calculus.

Biliary colic is accompanied by jaundice or distension of the gall-bladder. Affections of the urinary bladder, which might be confused with renal calculus, may be cleared up with the sound or the cystoscope, or by digital examination. General diseases like locomotor ataxy, malaria, and hysteria, are sometimes accompanied by pain which might be confounded with that of renal calculus; but the other features of these diseases are characteristic of their origin.

The haematuria of renal calculus holds an intermediate position as

regards quantity between that of papilloma of the renal pelvis and malignant disease of the kidney and that due to tuberculosis : in the former it is extremely free, whilst in the latter it is little more than streaks incorporated in the mucus or pus present in the urine. Moreover, in these cases the haemorrhage is spontaneous, and not usually associated with any increase in pain ; whereas in calculus the attacks of haemorrhage are provoked by movement or jolting, and are immediately relieved by rest, which is not observed in the other cases. Paroxysms or exacerbations of pain also are a usual accompaniment. Tumour in the lumbar region, due to nephrectasis, may be more rapid in formation and rate of increase, and is accompanied by more pain than the tumour due to tuberculous or malignant disease ; and there may be antecedent symptoms pointing to the existence of calculus, or to calculous diathesis, before swelling begins.

When anuria occurs, the probability of its being due to calculus is great if the onset be sudden, and if pain or swelling be limited to one loin, and tenderness be discovered along the course of the corresponding ureter. This indication is strengthened by a previous history of calculus on the other side. All urinary calculi give a shadow with the Röntgen rays, some more intense than others ; thus xanthine and cystine and calcium oxalate and phosphatic calculi all give a dark shadow ; whilst uric acid and calculi composed of urates give a much less pronounced effect. The x-rays at the present day, in the hands of competent men, afford an all but infallible guide to the diagnosis, provided due care is taken to remove any doubt as to whether a shadow which may be cast in the position of the kidney, or along the line of the ureter, is or is not due to something in the intestine, or otherwise outside the urinary tract, such as a cretified lymphatic gland.

Treatment.—This may be prophylactic, palliative, and surgical.

(i.) **Prophylaxis.**—The food must be moderate in amount, and carefully selected ; animal diet is to be used in moderation, an excess of nitrogenous food avoided, and diluents taken liberally.

(ii.) **Palliative treatment.**—Alkaline drinks, if the urine is decidedly acid, or distilled water are to be used freely, and saline aperients as required. During an attack of renal colic, the hot bath, opium, or belladonna fomentations, subcutaneous injections of morphine, or suppositories of belladonna and morphine are the means of relief. In very severe cases the inhalation of chloroform has been of use. Warm diluent drinks may be given, and the patient should lie with the shoulders and thighs raised.

In infants Dr. R. A. Gibbons has described the effects of uric acid concretions in their passage down the ureter. The testicle is drawn up ; there is evidence of great pain and tenderness on the corresponding side of the abdomen ; the urine is clear, scanty, and passed frequently in small quantities with considerable pain, accompanied by minute cayenne-pepper-like grains of uric acid, and sometimes a little blood. There is more or less incontinence of urine both by night and day. True calculi,

according to Henoch, are as common in children as in adults; but in their passage down the ureter the child suffers much less pain than the adult. The stone is composed of uric acid, and the subjects of stone are always the offspring of gouty parents, and for the most part are males. The attacks of renal colic occur with remarkable suddenness, and without any premonitory signs of illness. These cases should be treated by hot baths, followed by poultices or fomentations to the loin on the affected side, and the administration of a mixture containing bromide of ammonium, sal volatile, and compound tincture of camphor. In older children it has been found that a mixed ordinary diet combined with tonics and an abundance of fresh air afford the most effective means of combating the defective metabolism which results in the excessive formation, and separation, of uric acids and urates.

(iii.) Surgical treatment.—When the symptoms of stone are severe, and are not removed or rendered bearable by five or six months of medicinal treatment and rest; when, in order to diminish pain or haematuria, the patient is compelled to confine himself to the recumbent posture; or when anuria supervenes upon the symptoms of calculus in one or both kidneys, *nephrolithotomy* is indicated. The object of this operation is to save the kidney. If, however, the organ is in great part destroyed, if there is calculous pyelitis, or calculous hydronephrosis or pyonephrosis, *nephrotomy* and extraction of the stone are the necessary measures.

If, after the kidney and ureter have been thoroughly explored—not only over the outer surface, but by digital examination of the interior of the renal cavity—a stone cannot be detected, and yet the symptoms point definitely to the presence of stone, and the patient's life is insufferable from pain or haemorrhage, *nephrectomy* is the last resource. But this can only in very exceptional cases be justifiable, unless the kidney is very largely disorganised.

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XVI. CALCULOUS ANURIA is the gravest and most rapidly fatal of the many serious complications of renal calculus.

The principles of its treatment were not until the last twenty years properly recognised, and even at the present time are too seldom acted upon. So far, however, the more frequent resort to operative treatment has reduced the mortality nearly 50 per cent, the percentage of recoveries in cases operated upon being 51 per cent, whilst in those not operated upon it is 20·8 per cent.

Etiology.—Calculous anuria is produced by a stone in the kidney or its ureter causing sudden obstruction of the only functionally active kidney. The kidney of the other side may be absent or atrophied or utterly destroyed by renal calculus or some other affection. If the renal structure of this second kidney has not been utterly destroyed, but has been taking some part in the excretion of urine up to the moment of obstruction of the active organ, its function will be suppressed by the reno-reflex influence. It is not unknown, but it is rare, that both kidneys, having been previously active, have become simultaneously and similarly obstructed by calculi. Calculous anuria may occur at any age and in either sex; it is, however, more frequent in males of 35 years and upwards; but instances of children, and even of infants at the breast, dying of convulsions from calculous suppression have been recorded. Gout is a disposing cause. The immediate cause of the anuria is anything which leads to the shifting of a quiescent or fixed calculus into the renal pelvis, where it blocks the upper orifice of the ureter, or into the ureter itself, in any part of which it may become impacted.

Pathological Anatomy.—Apart from the rare instances in which both ureters become simultaneously occluded, and the less rare cases in which one kidney is the seat of calculi and the ureter of the other becomes blocked, there are two of three pathological conditions present in calculous anuria: (1) either the congenital absence or atrophy of one of the kidneys; or (2) its complete or nearly complete destruction as a secreting organ by some form of disease; and (3) the mechanical obstruction by a calculus or several calculi of the other kidney or its ureter. A minute calculus weighing not more than 1½ grs. may suddenly block the ureter of a perfectly normal kidney and thus produce anuria; or the renal substance of the only functionally active kidney may become gradually destroyed till complete suppression of function is reached, giving rise to the so-called "anurie calculeuse toxique." Fatal calculous anuria is not known to have ever occurred from obstruction in one kidney or its ureter when the other kidney and ureter have been normal. It has often been stated, however, that anuria is produced by a calculus in one ureter causing reflex suppression in the opposite normal kidney as well as obstructive suppression in its own. It is doubtful whether such an effect ever lasts more than a few hours, and there is nothing to prove that it has ever led to a fatal result.

Symptoms.—Anuria due to calculus often affects individuals in robust health. There are two classes of persons liable to the affection—

namely, stout robust adults past middle age, and thin dyspeptic and nervous persons. Commonly the subjects of calculous anuria have had attacks of renal colic, or other symptoms indicative of renal calculus, for months or years prior to the attack which brings on the anuria; and these previous attacks are usually described as having concerned the opposite organ and not the side now affected.

The symptoms of the anuria are not simply those of uraemia; and the uraemic symptoms when they set in are very different from those of the uraemia in Bright's disease and other forms of nephritis and lardaceous disease. The onset is usually sudden, the patient having been going about in his usual health up to the moment he is seized with renal colic. In rare instances the onset is insidious, but in most cases pain in the region of the kidney immediately involved is experienced at the very commencement and may continue throughout the anuria, though more commonly it subsides about the second day. When there is hydronephrosis of the involved kidney anuria is accompanied by persisting pain. With the pain may be a continual desire to micturate though not a drop of urine may be in the bladder, or, if any, only a few drops or teaspoonfuls of bloody urine. Or there may be polyuria, the urine being pale and of very low specific gravity, shewing evidence of imperfect obstruction as well as of imperfect renal function. In other cases the anuria has been incomplete, or intermittent, ceasing after a few hours or a few days to reappear and become definitively established. The anuria may last many days without the occurrence of uraemia; this is perhaps its most characteristic feature, but one which the calculous form shares with other forms of obstructive anuria, as distinct from the non-obstructive forms. Even when the suppression is complete, seven, eight, or ten days may pass before symptoms of uraemia appear, and in some cases death has occurred without their appearing at all. When uraemia supervenes death follows quickly, or at any rate within one or two days.

When the active kidney is hydronephrotic the uraemic condition may be deferred for a still longer period, even if there are no polyuric intermissions. Such remissions have marked the course of several cases on record; in one there was a succession of them, and the fatal termination was thereby deferred until the thirtieth day from the onset; in another there was one exhibition of polyuria on the thirteenth day, and death was postponed until the twenty-second day.

In the prae-uraemic stage the patient, though he may not pass a drop of urine for several days, may yet walk about, eat, and do mental work with all the appearance of good health. This must never be forgotten if a serious error in diagnosis and prognosis is to be avoided. It is, however, all the more likely to escape attention, because it is so different to the state of things in the much more frequent cases of suppression of urine due to non-obstructive causes. In the non-obstructive cases there will be symptoms of uraemic poisoning, and death may occur within twelve or twenty-four hours; and if the suppression ceases the return of the urinary excretion is gradual, and the

urine at first excreted is scanty, albuminous, and probably bloody. In calculous anuria, on the other hand, the suppression may be complete for many days, as just stated, without causing any uraemic symptoms; and if the excretion returns either temporarily or permanently, the urine is at once passed freely, is of low specific gravity, is generally pale in colour, though it may contain blood or albumin, and is defective in the ordinary urinary constituents.

When there is hydronephrosis of the kidney last involved, there will be either a gradually increasing or an intermittent tumour in the corresponding lumbar region. This should always be examined for, as an overlooked hydronephrotic kidney in calculous anuria sometimes ruptures. Moreover, it is in these cases that early operative treatment is most successful.

In the uraemic stage the pulse is slow and full and later becomes irregular; the temperature is 97° to 98° F.; and epistaxis, oedema, and venous stasis have been observed. Profuse perspirations may occur but not in the last day or two of life; or in their absence there may be itching of the skin and profuse salivation. Vomiting may be copious, and is a symptom of bad omen. Diarrhoea is very exceptional, but on the contrary obstinate constipation and meteorism are common and troublesome symptoms. Contraction of the pupils and convulsive muscular tremors are marked effects of the uraemic poisoning, and nearly always indicate a fatal termination. The limbs instead of being affected by muscular tremors may be benumbed and as if paralysed. Occasionally the patient has died of coma or in a convulsive crisis, or in an attack of suffocation two or three days after the onset of the uraemia; other modes of death have been by respiratory or heart failure without a convulsion and without coma. When anuria is complete and continuous the uraemic stage usually supervenes about the seventh or eighth day.

Diagnosis.—The history of former attacks of renal colic on one or both sides, and the sudden onset of the anuria associated with pain in one of the renal regions, sufficiently indicate the cause as being of a calculous nature. This will be strengthened if the previous attacks of colic have been followed by the passage of gravel or fragments of a calculus. It should not be forgotten, however, that a kidney may become completely destroyed as a functional organ by latent or quiescent calculus. In the very exceptional cases in which the anuria occurs without pain on either side and without the history of previous attacks of colic, or when the patient has quite forgotten on which side he suffered the previous attacks, the surgeon may have no clinical symptom whatever to guide him as to which kidney was latest involved, and therefore as to which kidney or ureter to operate upon, and the x-rays, by shewing signs of calculus on both sides, may not be able to render him assistance. If other means fail, one, or each, of the kidneys should be explored by an incision in the loin. The distinctions between calculous uraemia and uraemia due to non-obstructive causes have been already described.

Prognosis.—The usual termination of calculous anuria when not surgically treated is death about the tenth or eleventh day. This at least is the fate of rather more than 75 per cent of the cases. The chances of spontaneous recovery diminish with the prolongation of the anuria. Spontaneous recovery is announced by an abundant polyuria, or by the passage of gravel, blood-clot, or calculi; and it is often preceded by the free action of the bowels or by an abundant escape of intestinal gas. Spontaneous recovery may be complete and permanent if the calculus which caused it has escaped by the ureter; when the cause rests within the kidney or ureter there will in all probability be a relapse sooner or later.

The treatment up to twenty years ago or thereabout was entirely medical, by purgatives, diuretics, diaphoretics, and antispasmodic drugs, aided by hot baths, forced exercises, and massage. The results may be fairly stated to have been death in 79·2 per cent of cases. The only hopeful treatment is nephrotomy—in the gravest cases to prevent death from suppression, in the milder and in the intermittent cases to extract the calculus which otherwise may produce fatal anuria. The functionless condition or absence of the second kidney is an additional reason for nephrotomy, not a contra-indication as has been too often supposed.

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XVII. NEW GROWTHS OF THE RENAL PARENCHYMA.—A. Solid New Growths.—The kidney is liable to many morbid growths of a cystic and solid character, both benign and malignant. Several of these do not attain to any great size, or cause the kidney to become appreciably, if at all, enlarged. Thus, *adenoma*, which occurs in three forms in the kidney (the tubular, the papillary, and the alveolar), is usually the size of a hazel-nut or walnut, and seldom, if ever, so large as an egg or small orange; *cavernous angiomas*, though distinct formations or new growths of reticulated cavernous tissue, are of quite small size, not exceeding that of a marble, and, though called tumours, the parts which they affect are often shrunken, rather than projecting or enlarged; *leukaemic tumours* are small, scattered, roundish patches of lymph-cells following the course of the capillary vessels; *lymphadenoma* is found in the kidney, associated

with similar disease of the glands, liver, and intestine ; *fibroma* occurs "in the form of small white knots of fibrous tissue near the bases of the pyramids" (Moxon) ; Genewein considers that the small fibromas commonly seen in the medulla are not tumours in the ordinary sense, but fetal malformations, and calls them hamartoma fibrocanaliculare ; tumours consisting of a mixture of *fatty tissue and unstriped muscular fibres* are small growths, single or multiple, which rarely surpass the size of a cherry ; various-sized and numerous cysts, as in *granular kidney*, may be present without adding to the size of the organ. *Villous papilloma* occurs in the renal pelvis, as does also *carcinoma* with a villous character.

Though pathologically of the nature of "tumours," yet, clinically speaking, some of the above-mentioned formations never give rise to actual tumours ; others do so but rarely.

Morbid new growths of the kidney occur (1) in the renal parenchyma, (2) in the renal cavity, *i.e.* within the calyces and renal pelvis, (3) in connexion with the outer surface of the renal capsule and in the perinephric tissue. Those under this third heading include what are called the perinephric and paranephric tumours, as well as tumours of the suprarenal capsule and those originating in remains of the Wolffian body, or in adrenal or renal "rests" in the outlying cellular tissue around the kidney or in the hilum of the organ.

Malignant Disease of the Kidney.—*Pathology.*—Malignant tumours of the kidney include several different forms of new growth. The larger number are sarcomas, which appear at the extremes of life. Of 67 cases of malignant disease collected by Sir William Roberts, 25 occurred in children under ten years, 3 only of these after five. These infantile tumours are almost invariably sarcomatous, and are remarkable for the rapidity of their growth and the enormous size to which they attain : Sir Spencer Wells recorded a tumour removed from a child of four, weighing nearly 17 lbs., and others have been found exceeding 30 lbs. in weight. Sometimes both organs are invaded at the same time. Of 67 instances quoted above, 60 were unilateral, and in 3 only was it clear that the disease was primary on both sides. According to Guillet, from observations chiefly made after death, only 7 out of 72 cases were bilateral. In 1880 Dr. Abercrombie exhibited three cases at the Pathological Society in which both kidneys in children were invaded from the hilum by sarcoma. The incidence of malignant disease appears to be pretty equally distributed on the two sides ; but as regards the influence of sex there is a remarkable preponderance in males, the proportion being as 47 to 19 (64 to 35, according to Guillet). This disproportion in distribution is not so well marked in the case of children, the proportion of males to females being as 15 to 9 in those affected up to ten years of age.

In children growth is extremely rapid, metastasis occurs early, and death usually results within a year. The distribution of the secondary growths takes place with nearly equal frequency in the lymphatic glands,

the lungs, and liver. Of 154 cases of renal new growths which I collected from English, American, and foreign literature over a period of ten years, the nature of the growths was as follows:—Sarcoma, 63; carcinoma, 41; adenoma, 10; papilloma, 3; myxoma, 2; lipoma, 2; hydatid cysts, 11; dermoid cyst, 1; polycystic disease, 21. The following are the relative number of cases of tumours, solid and cystic, at different ages at which renal new growths occurred in 148 cases:—

Under 5 years.	5-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80
39	2	6	14	20	30	22	11	4

Sarcoma supplies by far the greatest number of malignant tumours; it occurs either before the age of five, in which case the disease may be bilateral, or at any subsequent age when they are unilateral and of somewhat slower growth. Of 39 cases in children under five years of age there were 31 of sarcoma, 2 of carcinoma, 1 polycystic disease, 1 fibrocystic, 1 rhabdomyosarcoma, 2 were tumours of the adrenal character, and 1 was of doubtful nature.

In infancy, sarcomas are usually encapsulated, and for the most part, in causing enlargement, do not alter the shape of the gland. Their growth is very rapid and the size attained enormous. The glandular substance of the kidney is almost completely destroyed. These tumours are composed either of round or spindle cells with groups of tubules between; and in some cases there are present also large fusiform cells with cross striation, having under the microscope the appearance of muscle fibre. The enlargement is painless, haematuria is rare, and secondary nodules form early in other organs. Removal of the tumour is not a very favourable operation, as young children do not bear interference with the viscera well, and many of those who have survived the operation have died from recurrence within a year. Still, the improvements in operations generally, and increased experience in renal surgery in particular, have in recent years reduced the mortality more than two-thirds, viz. from 60 per cent in 1890 to 40 per cent in 1894, and thence to 17 per cent in 1898. Operation for all forms of malignant tumours in children should be restricted to the earlier stages and to growths of medium or small size before the perinephric tissue or the lymphatic glands have become invaded. Tumours of large size and those which have infiltrated the surrounding tissues should not be touched. Adhesion to these rules has not only led to improvement in the operative mortality, but also in the distant results, and thus to an increase in the number of patients who survive not one year only but several years after the operation without recurrence.

Sarcoma in adults is for the most part composed of fusiform cells, and from the admixture of large striated fibres in bundles is in some instances called myosarcoma. Alveolar and spindle-celled sarcomas are also met with. One side only is attacked; haematuria occurs frequently, and large quantities of blood are lost at a time. The tumour rapidly attains a large size, and is accompanied by considerable pain, and

secondary deposits occur in other organs. The results of operation have until recently not been very much better than in children, death commonly occurring within a year of nephrectomy. This has nevertheless been performed in many instances on account of the pain and inconvenience of the swelling.

Other allied forms—such as *melanotic sarcoma*, which is almost invariably secondary in the kidney; *myxosarcoma*, in which the tumour is soft and jelly-like and of very rapid growth; and *lymphosarcoma*, which is scarcely ever limited to the kidney—are all extremely rare.

Carcinoma for the most part affects the kidney in the encephaloid form. It arises in the cortex and invades the rest of the organ, usually beginning at one pole; the growth is of the consistence of normal brain substance, pale, not very vascular, and generally encapsulated. The mass is seldom quite uniform, being occupied by areas of liquefaction, of colloid degeneration, or extensive haemorrhages; and in rare instances by induration of the nature of scirrhus. Carcinoma commencing in the lining membrane of the tubules also occurs, but not frequently. I have known this form to attain to a great size and to resemble in naked-eye appearances a semi-liquefied tuberculous mass (*vide p. 689*).

The cells of which the growth is composed are more often cylindrically arranged, and are columnar in shape, with rounded free extremities and a clear protoplasm. Both the cells and their arrangement resemble very closely what obtains in the convoluted tubes, even to the maintenance of a central lumen; and this is accurately repeated in the secondary deposits.

Instances are upon record of primary squamous-celled carcinoma of the kidney. In a case published by Robin, and quoted by Roberts, the cells resembled the pavement variety, and were remarkable for their size, measuring $\frac{1}{10}$ th of a millimetre in length. No nests were found as in an ordinary cutaneous epithelioma. In another case, recorded in the Middlesex Hospital Report for 1892, the tumour of the left kidney weighed 28 lbs., the bulk being due largely to calculous pyonephrosis; there was in addition soft new growth arising in the pelvis of the kidney, and secondary deposits in the lungs, liver, and retroperitoneal glands, all of which possessed the microscopical features of squamous carcinoma. The patient was a woman of eighty-two. In this case the origin of the new growth appears comparable to that arising in the gall-bladder in connexion with gall-stones.

Another form of carcinoma, called "*Épithélioma à cellules claires*," has been described by Albarran, in which there are parts with clear cells and others having the tubular structure exactly like the ordinary form of carcinoma.

Carcinoma attacks the kidney twice as often in men as in women, and usually in the latter half of life, nearly all the cases occurring after forty-five. Cancer has a more protracted course in the kidney than it generally runs in other abdominal organs, lasting in some cases four or five years or even longer, and resulting in a tumour of enormous size,

weighing 15 to 20 or more lbs. In the Middlesex Hospital Museum there is a cancerous tumour weighing 31 lbs. from the left kidney of a boy aged eight years.

Symptoms and Diagnosis.—Malignant growths of the kidney are for the most part rounded, smooth, or lobulated, and without the sharp edge possessed by the spleen or liver; in the infiltrating forms the tumour retains something of the original shape of the kidney, though no trace of the glandular substance may remain. With the exception of the comparatively rare cases in which the kidney is invaded by sarcomatous growth from the hilum, the new development almost invariably begins in the cortex and spreads thence to the pyramids; sometimes it invades the pelvis, ureter, or renal vein, or even the vena cava. In this way, or by pressure on or infiltration of the walls of the vena cava or aorta, obstruction is caused which may lead to oedema or gangrene of the lower extremities.

As a general rule the tumour is contained within the proper capsule of the kidney, which may be thickened and covered with dilated veins, or may be continued by fibrous tracts and dissements into the substance of the new growth, rendering attempts at intracapsular enucleation dangerous or impossible. In exceptional cases the capsule is perforated, and neighbouring organs or the parietes are infected by continuity. The consistence of the mass is affected by caseous, fatty, or colloid degeneration of its substance, or by extensive haemorrhagic effusion.

Tumours of the kidney occupy a characteristic position deep in either lumbar region, for the most part high up within the cavity of the abdomen; but when small and non-adherent, they descend with inspiration; when large, they extend towards the pelvis and across the middle line of the abdomen. There is often some bulging in the loin, and in any case the mass should be more easily felt from behind, and should play freely between the hands placed over the abdomen and the loin. The descent of a renal tumour on inspiration, though distinct enough to distinguish it from a swelling of pelvic origin, is very much more limited than in the case of the liver, spleen, or stomach, or growths connected with them; and lateral movement is practically not permitted at all. The intestines lie towards the centre of the abdomen, the tumour being close up to the flank, with the colon in front; and, if the mass be not too large, there is an area of resonance above and below it, separating it from the liver above, and continuous with the resonance in the hypogastrium below.

Very large tumours on the left side may cause varicocele and may displace the spleen and stomach towards or beyond the middle line, and on the right side may reach the diaphragm, displacing and tilting the liver, so that its edge occupies a vertical instead of a horizontal position near the middle line of the abdomen.

In the majority of cases the growth begins at one or other extremity of the kidney, more often at the upper. The mass formed is then definitely encapsuled, and when small and situated deep under the margin of the thorax is very difficult to make out. But as these are the

cases which are most favourable for operative treatment, the tumour and kidney being usually readily separated and unattended, in the early stage at least, by secondary growths, it is of the utmost importance to diagnose them early. Their presence is indicated, before the recognition of a tumour, by haematuria, often very profuse and coming on independently of shock or exertion; and by pain, tenderness, or discomfort in one or other loin. Haematuria occurs as the first symptom in at least 50 per cent of all cases of malignant tumour in the adult; but growths which commence in the hilum or just beneath the renal capsule, or deeper in the cortex, or even in the pyramidal parts of the kidney, but without early affecting the papillae, calyces, or renal pelvis, may appear as a tumour before producing haematuria. In 23 per cent of cases in the adult a tumour was the first discoverable symptom. It is neither so early nor so frequently to be detected in the adult as in children, but must be carefully sought for by palpation. With the aid of a thorough examination, under an anaesthetic if necessary, even a small swelling can be made out through thin abdominal walls; and this, together with the other symptoms, is sufficient to warrant an exploratory incision which may finally shew the necessity for removal of the kidney. As a rule the urine offers no indication of the presence or nature of a new growth. In some cases the quantity is rather increased or diminished, and in rare instances particles of the growth have been passed and detected in the urine. Growths of the kidney, like renal calculus, may cause such frequency of micturition and reflex irritation of the neck of the bladder, that the bladder and not the kidney is erroneously supposed to be the seat of disease, and, I am sorry to say, too often treated as such.

As regards *treatment*, most of the cases offer no hope of cure, the disease not being discovered till too far advanced for eradication. In cases which are diagnosed early, before secondary infection has occurred, nephrectomy may be performed with some hope of cure. Of late the mortality after nephrectomy for malignant disease of the kidney has been reduced from between 68 and 72 per cent, at which it stood in 1889, to 20 and 25 per cent which has been realised during the last ten years. Possibly this last death-rate is not likely to be much further diminished. Even now the duration of life free from recurrence in the survivors after the operation is but short in most cases, although patients are still alive and free of recurrence upon whom I operated in 1899 and 1901.

The principles which guide us in dealing with any given case are the same as those which we follow in regard to cancer of the mammary gland, and, indeed, of malignant disease generally.

It is only in exceptional cases, in which, for instance, death is threatened by haemorrhage or pressure effects, or in which the pain is unendurable, that *nephrectomy* is justifiable when we know that infiltrated tissues or infected lymph-glands must be left behind.

Partial nephrectomy has been performed for malignant new growths in some half-dozen cases, but in every case the surgeon thought he had a

benign tumour to deal with. The results of partial nephrectomy have not been encouraging. Total nephrectomy should be performed in cases of even very small tumours the malignant nature of which is evident or probable.

Benign Tumours.—Benign new growths in the kidney are very rare, and scarcely form 6 per cent of renal tumours. They are perhaps of pathological rather than clinical interest, inasmuch as they are usually discovered at necropsies, and do not often give rise to haematuria, tumour, pain, or any other symptom. When of large size they cause pressure symptoms, and are likely to be mistaken for ovarian or hydatid tumours or malignant new growths of the kidney. The *treatment* is either partial or total nephrectomy—partial, when the growth is small and clearly benign, a point, however, upon which the naked eye is far from being a sure guide. The prognosis after recovery is good in cases of simple fibroma and simple lipoma; but not so when sarcomatous or myxomatous elements are combined with the fibrous or the fatty tissue.

Myxoma sometimes attacks the kidney and rapidly develops into a large soft tumour. A case of this sort, occurring in a man of thirty-nine, causing death within a year from the first discovery of the tumour, without metastasis or haematuria, and with symptoms only of pressure and wasting with some abdominal pain, is recorded in the Middlesex Hospital Report for 1895. *Lymphangioma* is very rare. It consists of small soft nodes of connective tissue limiting small cavities filled with pigmentary and fatty granules. *Angioma*, or simple naevus, is very rare; it varies in size from a cherry-stone to a walnut or larger; it may or may not be encapsulated, and may be situated either in the medullary substance or immediately beneath the capsule. I have reported a case in which death occurred from haemorrhages and coma, in the first volume of my work on diseases of the kidney. *Lipoma* and *fibroma* of the renal cortex are apt to be mistaken for adenoma. They may be composed of true fatty or fibrous tissue respectively; or either may be mixed with other elements or contain cysts. They are usually small, but in certain instances have attained to great size.

Adenoma occurs in the renal parenchyma in three forms, namely, the tubular, papillary, and the alveolar. They are usually of quite small size, and may be single or multiple, and may be found in both kidneys of the same subject—usually in persons of adult age. They are apt to become malignant and to give rise to metastases.

Osteoma.—Many of the so-called bony growths are in reality calcified inflammatory products, transformed hydatids, or ossified fibromas.

Hypernephroma.—Of late a certain group of renal tumours have been classified from a genetic, not from a morphological point of view, under the name hypernephroma (*vide p. 427*). These tumours are situated just beneath the renal capsule, and are probably derived from "rests" or small aberrant masses of adrenal tissue. They resemble the malignant tumours of the adrenal gland itself; there is no transition structure between the growth and the surrounding renal structures, the tumour cells resemble

those of the adrenal cortex, and the growth is apt to extend along and to invade the venous rather than the lymphatic channels (Thorndike and Cunningham). Several other characters of the growths suggest the adrenal origin of the tumours besides those here mentioned. These tumours are more common in males than in females, and between the fortieth and fiftieth years of life ; they attain to a large size, are entirely within the capsule of the kidney, and encroach upon and destroy the renal parenchyma by pressure. The function of the kidney may for a time be little or not at all interfered with, but the tumour grows rapidly and impairs the function by compression. It is usually of a malignant, but sometimes of a benign character. When malignant it is apt to invade the renal vein and the vena cava, and to give rise to metastases in the lungs, liver, and bones ; metastasis in bone may be the first sign of a hypernephroma ; Scudder says that a bone tumour in a middle-aged or elderly person should suggest a metastatic hypernephroma. A bone metastasis may be the only one present. These growths are soft and "marrow-like," are well capsulated, and rarely invade the renal pelvis, and therefore rarely produce haematuria. They are very vascular, and have a pronounced tendency to marked interstitial haemorrhages, leading to cyst formation (Noble and Wayne Badcock).

B. Cysts.—Simple or serous cysts, which are met with for the most part in the kidneys of elderly people, may attain considerable size, and so constitute a troublesome disease. They cause no symptoms except those due to their size and to the pressure they exert on surrounding organs.

These simple cysts arise in the cortex of the organ, and project in relief from its surface, the rest of the kidney being healthy and functionally active ; or it may be granular, or more or less atrophied from the pressure of the cyst itself. Sometimes a communication is established between the cyst and one of the calyces of the kidney.

The contents of the cyst are fluid, containing a small quantity of albumin and a little saline matter ; but rarely, if ever, any urinary ingredients. Occasionally they contain blood from the rupture of blood-vessels in their walls, and sometimes a jelly-like or colloid material.

Their exact mode of origin is uncertain.

Symptoms.—Simple renal cysts begin insidiously, grow slowly, present themselves first in the loin, or in the lumbar area of the front of the belly, and may be so hard at first as to be mistaken for solid growths. As they increase, they gradually encroach upon the greater part of the abdominal cavity ; their point of attachment ceases to be even approximately ascertainable. As they grow they tend to spread out the renal substance, so that a good part of the kidney may be stretched in a thin layer over the attached part of the cyst wall.

Diagnosis.—The difficulties which surround the diagnosis of these very rare cysts are extremely great ; for not only may they be mistaken for hydatid of the kidney, hydronephrosis, and other renal tumours and perinephric fluid collections, but it may also be almost impossible to dis-

tinguish them from solid tumours in the parietes, from hepatic or splenic cysts, or cysts of the omentum, mesentery, or pancreas, from malignant cystic tumours springing from the pelvis or elsewhere within the belly, and, sometimes in women, from ovarian cysts.

Treatment.—When they become so large as to be inconvenient they should be tapped; if they refill, they should be laid open and the edges of the cyst stitched to those of the wound: the cyst will then collapse, and probably close. Removal of the cyst wall is preferable when possible. Smaller cysts should be excised from the kidney.

Polyeystic Disease; General Cystic Degeneration of the Adult Kidney.—The whole kidney is converted into a vast number of conglomeration of cysts of varying size, which leave scarcely any portion of the glandular structure unchanged, and give a greatly increased bulk to the organ, which, while retaining the renal shape, may be ten times the size of the normal kidney.

The place of the cortical and medullary portions are alike taken by the cysts which bulge the capsule and protrude on the surface as translucent sacs. The cysts vary in size from microscopic dimensions to that of a grape or walnut, the largest being often in the centre of the organ. The cysts do not communicate with the pelvis, calyces, or with each other. They are closed cavities, the walls of which are excessively thin, and lined by a delicate layer of epithelium. They owe their origin to expansion of parts of the uriniferous tubules, and they give rise to atrophy of the interstitial tissue. The original renal substance is in some places wholly removed; in other places small portions between the cysts remain unchanged. The fluids contained are clear, pale straw-coloured, dark yellow, purplish, or deeply blood-stained. In consistence these contents are limpid, serous, viscid, colloid, or turbid, caseous, and almost solid. Occasionally they are purulent; sometimes even solid, in which case they consist of molecules of fat, epithelium, and crystals of cholesterol, uric acid, or triple phosphates.

Sometimes the renal pelvis, but not the ureter, is much dilated. The dilatation is due, not to obstruction, but to dragging. In one of my cases the pelvis was enormously dilated. Both kidneys are commonly affected. The disease is very often associated with a similar cystic condition of the liver. Dr. Dickinson found only one case out of twenty-six in which the disease was confined to one kidney. In the early stages the cyst walls have a membrana propria, and are lined with tessellated epithelium, which in advanced specimens is difficult to detect. When the disease is not far advanced, the renal pelvis is easily recognised; but in the later stages it becomes filled with fatty tissue. The ureter is narrow and the vessels are small. Minor degrees of the affection are not incompatible with life, and several instances are known in which such kidneys have been found in adult individuals.

These "congeries of renal cysts" are sometimes congenital, and lead to enormous abdominal distension of the fetus in utero, with serious difficulty in parturition. Cystic degeneration is a cause of death of the

fetus in utero or during birth; and it is sometimes found associated with various malformations, such as talipes, cleft palate, and imperforate anus.

Pathogenesis.—Numerous hypotheses have been evoked to explain the development of this disease, and the greatest diversity of opinion exists amongst pathologists. Naunyn regarded the condition as one of adenoma. Mr. Shattock has advanced the opinion that in these kidneys there is a combination of the mesonephros (Wolfian body) with the metanephros (true kidney), and that the cysts may be regarded as arising in remnants of the mesonephros embedded in the true kidney. There is a good deal to be said in support of the view that the condition depends on obstruction of the urinary passages, and personally I am led to the conclusion that the cysts in the polycystic kidney, whether congenital and in the fetus, or in the adult, are in all cases alike of the nature of retention cysts and due to obstruction. In some cases the obstruction may be caused by fibrous proliferation around the tubules, in others to exudation into the tubules of some material which blocks them; in other cases again the tubules may become functionally isolated as the result of cicatrisation after nephritis, or of a congenital defect due to the failure of union of the secreting with the carrying-off parts of the kidney; but in all cases there is obstruction resulting in cystic dilatation.

Symptoms.—“The clinical history of this disease,” according to Wilks and Moxon, “is the same as that of chronic Bright’s disease, of which, notwithstanding their vastly different appearance, these enormous-looking tumours form only a variety. The cysts are, in short, an excessive production of that minute cystic condition of the kidney which we have already described as occurring in granular kidneys.” As with granular kidneys, so with the large cystic kidney, hypertrophy of the heart is not infrequently associated. In one of my cases the left ventricle was much hypertrophied, the right kidney was converted into a congeries of cysts, the secreting structure almost gone, and the pelvis enormously dilated; the left kidney was large and granular, had a wasted cortex, and was puckered in places on the surface.

The subjects of the large cystic kidney (not congenital) are more often men than women; and are always adults, the majority being persons at or past middle age. In six cases the ages of the patients were thirty-nine, fifty, sixty-five, two between thirty and forty, and one twenty-one years respectively. Out of 21 cases mentioned by Dickinson, the ages of 11 were between forty and forty-nine. In this form of disease there is no tendency to dropsical effusions; but pain in the loins and haematuria, especially the latter, are frequent and pronounced symptoms, and are useful in diagnosis. When oedema occurs in a case of cystic kidney, it is the mechanical effect of pressure of the tumour. The characters of the urine are like those of the granular kidney. It is pale in colour, abundant in quantity, of low specific gravity, and albuminous even when blood is absent. Coagula and granular casts are occasionally found in the urine, and more rarely pus in small amount.

However, the symptoms are not always very obvious. In one case, the specimen of which is in the Hunterian Museum, the patient died of apoplexy at sixty-seven; his vessels were atheromatous, but his heart weighed only $9\frac{1}{2}$ ounces. Both kidneys were enlarged and cystic; their state had not been recognised during life. In another case, the patient, a sailor aged fifty, presented symptoms of brain disease, became delirious, and died in a few days. Both kidneys were almost entirely converted into congeries of cysts. In a third case, a shoemaker had severe pain in the loins and along the course of the ureters for five years; his urine was scanty, and always mixed with blood or pus. The other symptoms were numbness of the right leg, frequent severe headache, and occasional oedema of the lower limbs. Both kidneys were large and cystic, and the ureters were dilated.

In the late stages of the disease, obstinate vomiting, convulsions, suppression of urine, and coma supervene, and then follows death. Death sometimes occurs from exhaustion brought on by haematuria; sometimes from bronchitis or pneumonia; sometimes from oedema of the lungs, and sometimes from some quite independent cause. Of three fatal cases in my list, one died of bronchitis, congestion of the lungs, and *morbus cordis*; one of epithelioma of the tonsil and soft palate; and the third of epithelioma of the penis. When death is caused immediately by the state of the kidneys, the manner of death is most frequently by uraemia. The progress of the disease is not usually very rapid, from two to five years being a common period.

Diagnosis.—When, with a sallow complexion, hypertrophy of the heart, and increased arterial pressure, there are the above-mentioned characters of the urine and a tumour in both renal regions, or a tumour in one and an increased fulness in the other, the diagnosis of "large cystic kidney" is pretty clearly indicated. I have often felt the irregular outline of the kidney due to the projections on its surface of some of the numerous cysts. The tumour will probably be yielding; but it does not fluctuate, and it presents the usual topographical characters of renal tumours in general.

Treatment.—This should be based upon the same principles as that of interstitial nephritis. Moderate stimulation of the skin and bowels, with the avoidance of excess of nitrogenous food or exposure to unnecessary cold or exertion, so as to keep the production of nitrogenous waste down to the lowest point while promoting elimination vicariously, constitute the best general methods. As regards drugs, a laxative mixture containing iron is the most efficacious; and if the heart shew signs of feebleness, strychnine and digitalis may be added with advantage.

The surgeon's aid will not often avail permanently owing to the frequency of the bilateral incidence of the disease; and when unilateral, unless the size be very inconvenient, or tension gives rise to pain and much suffering, no surgical treatment is called for. I have in several cases given great relief by cutting down upon the kidney and incising and evacuating the largest of the cysts. However, in two out of three

cases in which I have removed such kidneys the patients have recovered. A patient from whom I removed a polycystic kidney nearly fourteen years ago was known to be alive and well as recently as two years back, and I believe she is still living.

Hydatid cysts form tumours in connexion with the kidney. The kidney stands third in order amongst the viscera favoured by this parasite, being thus more frequently affected than any other organ or tissue of the body except the liver and lungs.

The left kidney seems to be affected nearly twice as frequently as the right, owing perhaps to the shortness and directness of its arterial branch. The cyst may be immediately beneath the capsule, or lodged deeply in the substance of the kidney. In either case, as it grows it forms an elastic, rounded, and sometimes fluctuating tumour projecting from the surface of the organ. The whole kidney may ultimately be destroyed by the cyst, which may come to fill a large part of the abdominal cavity; but in the majority of cases it remains quite small, and does not exceed the size of an egg or an orange, because the contents of the cysts find an escape by the ureter.

A renal hydatid cyst may burst into the pelvis of the kidney or into the intestine or lung. Sir William Roberts tells us that it has a natural tendency to discharge its contents by the ureter; and out of 63 cases collected by him, hydatids were discharged by the ureter in 52: in 47 the cysts opened into the pelvis of the kidney only; in 1 into the pelvis of the kidney and the lung; in 3 into the intestine; and in 1 into the stomach, as well as into the renal pelvis. In 1 case the opening was into the lung only; in 2 the cyst was opened artificially, and in 8 cases it did not open at all. Roberts states that there is no authenticated case of a hydatid cyst of the kidney opening in the loin, and that Rayer's two cases which so opened were hydatids in the muscular tissue of the lumbar region. In a third case there was post-mortem proof that the cyst was unconnected with the kidney.

Symptoms.—In some instances there are no symptoms, and the cyst is met with as a post-mortem surprise. In others there are no symptoms until the cyst bursts, after the common manner of the disease, into the renal pelvis, when attacks of renal colic begin and recur from the passage of the daughter cysts and portions of the hydatid membrane along the ureter. In a third class of cases there is an abdominal tumour, with or without the symptoms excited by the escape of the contents of the cyst along the urinary passages.

In 18 out of 63 cases, according to Roberts, a tumour in the side was discernible during life, and varied in size from an orange to an adult head. Fluctuation is not always to be detected, either because of the extreme tension of the cyst walls, or because of the small proportion of fluid to daughter and grand-daughter cysts. The hydatid thrill or fremitus has been seldom observed. The hydatids discharged by the urethra are in various states—broken or entire, as fragments, or as vesicles simply collapsed. There may be one or two only, or scores of vesicles. Some

contain only water, others have minute cysts within. Crystals of uric acid have been found adhering to them ; crystals of triple phosphate, uric acid, and oxalate of lime have been found within. When the parent cyst has suppurated before bursting, pus is discharged as well as hydatids. Blood is sometimes discharged in the urine. In a case of which I have notes, the cysts were mixed with large quantities of pus in the urine ; but some of the smaller and unruptured cysts contained the ordinary clear saline and non-albuminous fluid characteristic of hydatids. In some cases, hooklets, shreds of hydatid membrane, and oil particles, but no vesicles, are found in the urine.

In relation to the discharge of hydatids by the urethra, it must not be forgotten that hydatid cysts of the liver have sometimes discharged into the renal pelvis ; and hydatids in the cellular tissue of the pelvis, or in the track of the ureter, have broken into the bladder or ureter, and thus escaped by the urethra. Such cases are infinitely rare. Birkett knew of one case in which hydatids were withdrawn by a catheter from the bladder, the cysts having escaped into the bladder from a hydatid tumour between it and the rectum. Other similar cases of hydatid tumours in this situation opening into the bladder are on record ; but they are to be distinguished from hydatids in the kidney by the formation of a pelvic tumour, and by the prolonged and increasing pressure-effects upon the bladder and rectum. The escape of the vesicles may or may not excite nephritic colic. There may be one or several discharges at longer or shorter intervals of a few months or several years. Sometimes at the first escape the cyst empties itself and dries up ; in other cases there have been numerous periods of escape over many years, and at uncertain and very variable intervals.

Pain in the lumbar region and along the course of the ureter of the affected organ, with a sensation of something giving way, usually precedes the discharge. Rigors, vomiting, spasmodic colicky pains, and sometimes suppression of urine and retraction of the testicle, accompany the passage of the vesicles along the ureter, which takes from a few hours to several days to be accomplished ; then comes a period of relief during their stay in the bladder, and this is followed by the distress, retention, and painful efforts to micturate which indicate their journey through the urethra. An accident, such as a blow, kick, or fall, or the jolting of horseback or carriage exercise, may lead to the rupture of the tumour, and to the first or to any subsequent escape of the vesicles.

When a tumour exists, and is very large, it may fill the loin, and to a greater or less degree the corresponding side of the abdomen. It may be quite round and regular in outline, or present a somewhat nodulated surface. Its relations to the bowel and to the ribs and surface are the same, and are subjected to the same exceptions as renal tumours generally. In a case shewn to the Glasgow Pathological Society (Fotheringham) the patient had a nodulated tumour, which filled the right lumbar region, and caused pain and tenderness ; the ordinary symptoms of Bright's disease were also present. Within a fortnight, after suppurating and

discharging pus and cysts by the urethra, the symptoms of Bright's disease disappeared.

Suppuration may occur as the result of violence or of puncture; whether for the purpose of diagnosis or treatment, or independently of either. If it occurs, then rigors, fever, and increased pain and tension about the tumour set in.

Prognosis.—The prognosis of renal hydatids is not always unfavourable. Sir W. Roberts's list of 63 cases yields 20 in which recovery was believed to have been permanent, and 19 of which were fatal; in the remainder (24) the results were not known. In 10 of the fatal cases death was directly due to the hydatids bursting into the bronchi, to pleurisy, to the effects of pressure of the tumour, or to suppuration of the contents. In one case a large renal calculus was found with the hydatids in a solitary kidney, and the hydatid tumour opened into the renal pelvis, and thus obstructed the outflow of urine. In 9 cases the causes of death were unconnected with the hydatids.

The duration of the disease is uncertain, but often very much prolonged. Patients have gone on passing vesicles at intervals for twenty and even thirty years. There are no means, except by waiting, of telling whether more remain behind after some have escaped by the passages. If, when the cases are left untreated, the prognosis of hydatid tumours of the kidney is more favourable than that of similar tumours of other internal organs, it is because of the tendency to rupture into the renal pelvis. When the tumour is small, and situated in the central parts of the kidney, the evacuation is easy and safe. There is no fatal case on record in which the vesicles have escaped by the urethra from a renal hydatid cyst which had not given rise to an abdominal tumour. The discharge of pus with the vesicles is not necessarily unfavourable; patients have recovered when the quantities of pus discharged have been very great. When the cyst breaks into the pleura or bronchi the probability of recovery is not good; when into the bowel or stomach it is much more favourable. When the cyst grows continually, and does not burst in any direction, the dangers of a large tumour and of its pressure effects have to be met.

Diagnosis.—is made certain when, with a tumour in the renal region, there is a discharge by the urethra of hydatid vesicles or of the other products of hydatid tumour. If the cyst do not rupture into the renal pelvis the urine will present no evidence of the nature of the disease; and if a tumour exists without discharging its contents by the ureter there is nothing to point out the precise nature of the enlargement except the use of the aspiratory trocar. The renal origin of the swelling must be diagnosed by the same means as other renal tumours. When vesicles are voided but no tumour exists, nephritic colic generally indicates the locality of the hydatids.

Treatment.—When a tumour increases without discharging by the urethra the only proper treatment is to cut down upon the tumour, and having tapped and emptied it of its fluid contents, to incise it and stitch the edges of the cyst to the margins of the parietal wound. The cyst

should be opened from the loin if possible; if not, then at its most prominent or projecting point. When the kidney is very extensively affected, nephrectomy will be necessary. When there is no tumour, and hydatids are discharged by the urethra, no surgical treatment is absolutely needed unless renal colic is frequent and severe; but in my opinion it is distinctly better to explore the kidney and excise the cyst. (Cf. Vol. II. Part II. p. 1024.)

C.—NEW GROWTHS ORIGINATING IN THE RENAL PELVIS.—A great number of tumours originate within the pelvis of the kidney, but simple papilloma and carcinoma are by far the most common. Seventeen out of twenty-seven villous tumours were benign, the others malignant.

Pathology.—The most frequent form of carcinoma of the renal pelvis is the transitional-celled and squamous-celled carcinoma; less frequently cylindrical-celled carcinoma occurs, and in a large number of cases of this form the growth has a papillary character. Long-standing irritation, such as a calculus, leads to the development of simple or benign papilloma as well as of cancer. Transformations of the renal epithelium of an epidermic character result in what has been described as "urinary leucoplakia," and in some instances this leucoplakia of the renal pelvis and ureter has been the starting-point of squamous-celled carcinoma. Cases of sarcoma, myxosarcoma, lymphosarcoma, myosarcoma, melanotic sarcoma, and mixed sarcoma and carcinoma with papillary growth, have also been reported, and in one case multiple small simple cysts were found in the pelvis of the kidney and in the ureter. Psorospermosis, due to coccidia, has been met with in the renal pelvis (*vide* Vol. II. Part II. p. 827). In quite a number of the cases in which the new growths started in the renal pelvis they have spread into and along the ureter.

One of the commonest effects of a growth in the renal pelvis is nephrectasis, due either to retention of urine and its consequences, or to extravasation of blood, *i.e.* to hydronephrosis or haemato-nephrosis. The quantity of retained fluid may amount to many pints, and in one case the fluid ruptured into the pleura. These changes result equally from benign and malignant growths.

Diagnosis.—It will rarely be possible to distinguish clinically between tumours primarily of the renal pelvis and those commencing in some other part of the organ or in the ureter. An abdominal tumour of very considerable size may be caused by the tumour itself. When thus due to the new growth itself nothing in the outline of the abdominal tumour or in its mode or rate of increase will serve to distinguish it from a new growth of the renal parenchyma or capsule. When the abdominal tumour is due to nephrectasis the presence of other symptoms indicative of new growth will tend to exclude the commoner causes of hydro- and haemato-nephrosis. Such evidence of new growth as fragments of villous processes, a large number of cylindrical or pavement epithelial cells, or large spheroidal cells containing highly refractive granules in the urine,

would, in the absence of vesical new growth, indicate a papilloma of the ureter or renal pelvis as distinct from a tumour arising in the renal capsule or parenchyma. A cystoscopic examination may reveal a particle of growth projecting from the ureteral orifice, but it would not proclaim either the nature or the primary seat of the disease.

Symptoms.—A tumour, haemorrhage, and the characters of the urine are the symptoms of these new growths of the renal pelvis. *Pain* is an inconstant and rarely an early symptom, and when present is due to the passage of clots or particles of growth down the ureter, or to tension or the pressure effects of the tumour. *Nephrectasis* is one of the most frequent results, occurring in about two-thirds of the cases. Often the hydro- or hydro-haemato-nephrosis is intermittent. When blood alone is the cause of the distension intermittence in the swelling is improbable. *Haematuria* may be intermittent or continuous; it is usually the earliest symptom. It may be slight and intermittent at first, and later become continuous and so profuse as to threaten or actually to terminate life. The urine may contain nothing abnormal, or such characteristic substances as have just previously been described under "diagnosis." *Albuminuria* may precede, and intervene between, the attacks of haematuria. With new growths of the renal pelvis the urine may yield a heavy deposit, and contain pus in quite considerable quantity. The quantity of urine passed may be normal, or diminished, or increased. Death may occur from *uraemia*, or from anaemia, haemorrhage, or in malignant cases from multiple metastases.

The prognosis is unfavourable. The benign papillomas undoubtedly tend to become malignant after a time.

Treatment.—Nephrectomy performed in good time affords the only hope of cure. If from inspection or downward catheterisation of the ureter there is reason to believe that the ureter is invaded, nephroureterectomy is the operation of selection.

D.—NEW GROWTHS ORIGINATING IN THE RENAL CAPSULE, AND IN THE PERINEPHRIC AND PARANEPHRIC TISSUES.—Besides the new growths which take origin from the renal parenchyma, from adrenal "rests" within the fibrous capsule of the kidney, and from the interior of the renal pelvis, there are others which clinically so closely resemble true renal tumours as to be scarcely distinguishable from them and which pathologically it is often very difficult to differentiate from them. I refer to such as spring from the fibrous capsule of the kidney and grow outwards from it, and to others which start either in the perinephric or paranephric tissue.

No attempt will be made to mark off the tumours which arise in the perinephric tissue; that is, in the fatty tissue immediately around the kidney, between it and the retro-renal fascia, and packing the structures within the sinus or hilum of the organ, from those which arise in the fibro-fatty tissue behind the retro-renal fascia. They will here be all grouped under "paranephric solid tumours" and "paranephric cysts."

It must further be noticed that tumours originating in the suprarenal gland itself become in their progress, as do the paranephric new growths, clinically indistinguishable from renal new growths. Tumours of the adrenals are described on p. 427.

Paranephric Tumours originating in Renal or Adrenal "Rests."—Many of the paranephric tumours—cystic as well as solid—have their origin in adrenal "rests" which are known to be present not unfrequently in the tissues around the surfaces and within the hilum of the kidney. In the early weeks of the intra-uterine existence of the human fetus the lower end of the adrenal occupies the hilum of the kidney, and is continuous along the course of the ureter with the upper end of the Wolffian body. Even in the adult the suprarenal capsule is often prolonged into the hilum, and supernumerary adrenals have been found as low down as the broad ligament and the inguinal canal (*vide* p. 428). Retroperitoneal remains of the Wolffian body are accountable for many retroperitoneal cysts. Probably many tumours arise from aberrant renal lobules embedded in the fibrous capsule of the kidney and capable of becoming malignant. Such collections of embryonic renal tubes have been discovered in the renal capsules of a great number of fetuses.

Many of the paranephric new growths of adrenal origin have the kidney simply attached to them; others cause atrophy of the kidney from compression; others spread the kidney, which becomes intimately incorporated with them, over their surface; and others again penetrate the renal capsule or send offshoots into the hilum and infiltrate the organ. Thus, many both of the benign and malignant forms of paranephric new growths, after attaining a certain size, become indistinguishable from a new growth originating within the renal capsule.

Symptoms.—Little or nothing which is distinctive can be stated as to the symptoms and the means of diagnosis of paranephric as distinct from renal new growths. This is not surprising, considering the similarity of position of the tumours behind the peritoneum, the not unfrequent absence of haematuria in renal tumours—in 50 per cent—and its presence in paranephric tumours after they have penetrated within the fibrous capsule or the hilum of the kidney.

Paranephric Tumours of Connective-Tissue Type.—There are various other paranephric solid tumours besides those originating in fetal remnants. The connective-tissue tumours often vary in structure in their different parts. Thus, lipoma, fibroma, myxoma, sarcoma, and mixed forms spring from the tissue surrounding the kidney. Pure myxoma is very rare, myxosarcoma is less so. The most frequent kinds are fibrolipoma and myxolipoma.

Etiology.—The kidney may be more or less embedded in any of these paranephric tumours, or may be flattened or displaced by them, but it is rarely penetrated except by paranephric sarcoma. The sarcomas and mixed tumours (myxolipoma, chondrolipoma, lymphosarcoma) are met with most frequently in young persons, and occasionally in quite young children. The growths may be encapsulated or diffuse; if encapsulated,

several encapsulated masses may be welded together into one multilobed tumour. Other separate retroperitoneal growths, either of the same nature, or not of the same nature, may be coexistent with the paranephric growth. The colon and small intestines are sometimes intimately adherent to the tumour.

Many retroperitoneal lipomas are not paranephric, but it is probably not far wrong to say that about one-third of them have a peri-nephric origin. The *lipomas* are most common in adult life between thirty and fifty years of age, but they have been met with in children of three and in adults beyond seventy. They occur in the temperate, healthy, and hard-working; and are commoner in females than males. They are distinct neoplasms of fatty tissue, and are not to be confounded with those great overgrowths of fibro-fatty perinephric tissue which occur in connexion with renal calculi and other forms of chronic renal disease.

Several of the recorded paranephric *lipomas* are stated to have taken origin in the renal capsule. The size attained by some lipomas has been enormous, namely, from twenty to forty pounds in weight and upwards. They sometimes fluctuate, and then have been confounded with ovarian cystomas or *echinococcus* cysts. They are apt to undergo mucoid degeneration, and thus have been called *lipoma myxomatodes*. When instead of the typical connective or fibrous tissue, spindle-celled tissue separates the fatty lobes of these tumours a sarcomatous appearance results. Portions of the growth may suppurate and form large cavities full of greyish-green pus; sixty pints of such pus were drawn off in one case (Adami) (*vide also Vol. III. p. 980*).

Fibromas or *fibromyomas* are relatively common. They arise from the capsule proper of the kidney, which normally contains smooth muscle-fibres. Often not larger than a hazel-nut, they more frequently attain to a large size; a weight of forty-eight pounds has been reached. Being frequently very vascular serious haemorrhage has followed their puncture.

Myxomas may take the form of large cysts containing many ounces of gelatinous or mucoid, blood-stained fluid.

Sarcomas and *myosarcomas* are about as frequent as fibromas and fibromyomas. They originate most often from the capsule proper of the kidney, and may reach a considerable size.

Symptoms.—The symptoms are those of a tumour, sometimes of great dimensions, in the renal region, without, however, haematuria or other changes in the urine, unless, as in the case of sarcoma, the kidney itself becomes penetrated by the growth. The tumour varies very much in different cases in outline, hardness, mobility, and its pressure effects upon surrounding organs. It may be more movable than a very movable kidney, or it may be quite fixed by adhesions. When the mass consists of several encapsulated lobules, one portion of it may move on the rest. It may fluctuate and yet yield nothing on being punctured. It may occupy the greater part of the abdomen and descend into the pelvis and cause a prominence equal to that of advanced pregnancy, or it may grow upwards and encroach on the liver, spleen, or diaphragm. Some of the

fibromyomas are pedunculated and simulate a floating kidney. Pain is very rare, and, owing largely to this, patients refuse to submit to operation. Gastro-intestinal disturbances, such as obstruction, flatulence, colic, and indigestion, are not infrequent. Dyspnoea and extreme emaciation have been commonly observed as the tumours increased in volume.

Diagnosis.—A very slowly growing tumour causing little disturbance to health, giving a sense of fluctuation but yielding no fluid on puncture, crossed by a length of bowel, and progressively leading on to dyspnoea and emaciation, would suggest a paranephric lipoma. The sense of fluctuation would distinguish it from fibroma; and the rate of its growth from sarcoma and to a less extent from myxoma, though the diagnosis between lipoma and myxoma is admittedly very difficult. The negative result of puncture tends to exclude suppuration, ovarian and other cystic formations, and localised ascites. In one case a displaced kidney, associated with severe intestinal obstruction, gave rise to the mistaken diagnosis of an intussusception.

Prognosis.—When not sarcomatous the paranephric connective-tissue tumours are of slow growth and of long duration—from two to ten years and longer. In many there has been an entire absence not only of pain but of functional disturbance of any urinary, abdominal, or thoracic organ. Recurrence after removal is improbable, unless the tumour has a large sarcomatous element, or unless a separate, small encapsulated tumour which has been left behind takes on growth after the chief mass has been excised. Periodic attacks of intestinal obstruction may be caused, and necessitate removal of the growth. In the operation the greatest dangers are the complications arising from the overstretching of the intestines, and the detachment of the tumour from its adhesions.

Treatment.—It is only when these tumours have attained a very distinct size and are causing trouble by their weight, pressure effects, or disfigurement that the patients have sought surgical treatment. In the operation of excision the kidney may have to be sacrificed on account of its intimate connexions with the tumour. For this reason, and as the function of the kidney is not interfered with in the non-malignant varieties, operation should not be urged unless distressing or threatening symptoms are present.

Paranephric Cysts.—Besides those originating in adrenal “rests” or remnants of the Wolffian body, which have been already referred to, (1) serous cysts, (2) hydatid cysts, and (3) blood cysts have been described.

Serous Cysts.—Some of these have been closely connected with the renal capsule, and have communicated by a small passage with the renal calyces or pelvis; others have been quite separate from the kidney. Some of them have contained several pints of fluid. The fluid has been clear and watery, free of urinary constituents and albumin, except in one case in which it contained a little albumin and a trace of sodium chloride, but the cyst in this case had no communication with the intracapsular substance of the kidney. The treatment should be the removal of the cyst.

Hydatid cysts have been found in the perinephric tissue on every aspect of the kidney, and either adherent to the renal capsule or apart from it. The treatment should be excision of the entire cyst when feasible; but when situated between the kidney and liver, or between the kidney and peritoneum, and closely connected with the front surface of the organ, it will be better to open and drain, and stitch the edges of the cyst to the edges of the abdominal walls.

Blood Cysts.—These have been really false aneurysms due to rupture of a small aneurysm, or to the giving way of a diseased or ruptured vessel.

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XVIII. DIAGNOSIS OF RENAL FROM OTHER TUMOURS.—Renal tumours are among the most difficult of abdominal enlargements to diagnose correctly. The chief distinctive points about them are the following :—

1. The large intestine is in front of the tumour. Normally the right kidney, unless enlarged, lies a little way from the lateral wall of the abdomen, behind and to the inner side of the ascending colon ; not in close contact with the abdominal wall and outside the ascending colon, as the liver does. When enlarged, the ascending colon is usually placed in front of the tumour and towards the inner side of it. On the left side the descending colon is in front of the kidney, and inclines towards its outer side below. In some cases coils of small intestine may overlie a renal tumour, if the enlargement be not sufficient to bring the kidney into direct contact with the front abdominal wall. When the colon is empty or non-resonant, it can be felt as a roll on the front surface of the tumour, and the anterior walls can be felt to travel over the posterior as oblique pressure is made upon the gut. Bowel is never thus placed in front of a splenic tumour, and but rarely in front of one of hepatic origin. Rarely, if ascites is present, and the liver is enlarged in an irregular and misshapen manner, the small intestines may float between the liver and the abdominal parietes. As an exception, a right renal tumour may push the ascending colon down instead of bearing the gut forwards in front of itself. A tumour of either kidney may push the bowel to its inner side towards or even beyond the median line, in which case there is no resonance in front of the tumour.

2. There is no line of resonance between the kidney dulness and the vertebral spines, and no space between the kidney and the spinal groove into which the fingers can be dipped with but little resistance as there is between the spleen and the spine.

3. Renal tumours do not project or protrude backwards to any marked extent. They fill up the hollow of the loin, and may even cause some actual fulness there ; but often there is nothing more than the effacement of the natural hollow of the loin. When the tumour attains a large size the parietes may be projected laterally to a degree sufficient to be observed by a superficial glance. Sir William Jenner says : "Renal tumours never cause enlargement behind. A renal tumour is not visible in the back, it expands in front. A little greater fulness of the loin there may be, but nothing like tumour. . . . Tumours due to disease of the kidney enlarge in front ; whilst abscesses and other lesions which may simulate renal tumours often cause considerable posterior projection." A renal tumour may, however, as quite an exceptional event, cause pointing on the posterior aspect of the body. Holmes reported a case of pulsating cancer of the left kidney presenting a swelling over the sacrum, and causing oedema of the back as high as the neck.

4. "The kidney has no sharp edges. It is rounded on every side, and in disease never loses this peculiarity" (Jenner). Whether solid or cystic, and of whatever size, a kidney tumour is prone to retain some,

often much, of its natural outline. When the tumour occupies a part only of the organ, and not the whole, and therefore does not expand the entire capsule as it grows, it is unusual for it to have the renal outline.

5. Renal less frequently and less markedly than hepatic, splenic, and suprarenal swellings descend in inspiration. Hepatic and splenic enlargements, and more especially the latter, are depressed by the contraction of the diaphragm; whereas kidney swellings are often quite fixed in their position. If the kidney and circumrenal tissues have been inflamed, the kidney will be bound down in its natural situation, and there fixed; but in cases of new growth, in which the organ and parts around have not been the seats of inflammation, there may be a considerable degree of movement. I have seen a renal tumour descend as much as an inch by a deep inspiration, and fall forwards or backwards by its own weight with the movements of the body.

Mobility of the tumour in respiration and by palpation is so far from being rare that it ought hardly to be enumerated amongst the exceptional symptoms. .

6. As a rule, renal enlargements never invade the pelvis, rarely reach the median line, and frequently are separated from the hepatic dulness by a resonant area.

Either a cystic or solid renal tumour may ultimately attain such a size as to occupy the greater part of the abdomen. Numerous instances of this kind are recorded; but they attract attention long before this stage is reached, and while they are still limited to one side of the abdomen.

7. When the tumour is large enough to reach the front wall of the abdomen, the most anterior point at which it comes in contact with the parietes is commonly about the level of the umbilicus, or a little higher; the lateral wall between the costal margin and the crest of the ilium is then also bulged outwards.

When malignant growth or abscess affects part only of the kidney, the abdominal tumour may appear to be somewhat removed from the strict limits of the renal region. Thus, when the upper part of the kidney is alone involved, there is much upward bulging, and the tumour may be felt in the part usually occupied by the liver or spleen. In malignant disease of the right kidney I have seen the tumour occupy a great part of the right hypochondriac region, and simulate a hepatic tumour.

8. There is a symptom which occurs in large tumours of the left kidney, and not in splenic enlargements, namely, varicocele of the left side, which gradually increases with the growth of the tumour.

Little or no reliance can be placed on the absence of changes in the urine. Solid tumours do not always cause haematuria, nor do accumulations of pus in the kidney always cause a discharge of purulent urine. The tumour may not involve the cavity of the kidney, or the ureter may be temporarily or permanently plugged. Thus, the urine which is passed may all come from the other kidney and be quite normal. On the other hand, however, haematuria and pyuria associated with the physical signs of renal tumour are valuable adjuncts in forming a diagnosis.

To Estimate the Size of a Renal Swelling.—As the patient lies on his back, place the fingers of one hand flat upon the ileo-costal space just outside the erector spinae muscle, and those of the other hand flat on the front of the abdomen just over the hand which is behind. Then, during expiration, and while the patient's attention is diverted, a very fair idea will be obtained of the size and weight of the organ by depressing the fingers in front as much as possible, and tilting forwards those of the hand behind. In thin persons, and with the aid of an anaesthetic, this mode of examination is very effective. By its adoption a renal swelling too small to give rise to dulness on percussion will often be detected. Excepting in children and in persons much emaciated, a kidney which can be brought entirely within reach of the touch is either movable, misplaced, or diseased. Sir William Jenner pointed out that, when the lower dorsal and lumbar parts of the spine are curved well forwards, the kidney, even though only of natural size, may be sufficiently prominent to be seen through the abdominal parieties.

Diagnosis.—From enlargements of the liver.—Renal tumours often dip down or fade off so as to allow the fingers to be depressed between the edge of the costal cartilages and the upper border of the tumour. Hepatic tumours pass downwards from beneath the ribs, and so rarely do they have any intestine in front of them, that the presence of bowel in front of a tumour may be regarded as a strong indication that it has not its origin in the liver. The presence of jaundice is an important indication. A tumour in the concave part of the liver, especially a hydatid in the left lobe, is very likely to cause error in diagnosis, unless accompanied by jaundice. On the clinical confusion between movable kidney, enlarged kidney, and tumours of the gall-bladder the reader should refer to p. 245, and to a paper by the author.

From enlargements of the spleen.—The enlarged spleen has no bowel in front of it; it generally presents a sharp or well-defined edge, beneath which the fingers can be depressed; this edge is in some cases notched. There is resonance between the posterior edge of an enlarged spleen and the spinal column, and the tumour is traceable upwards beneath the ribs. A splenic tumour is movable; a renal tumour may be so, but often it is fixed in the loin. Splenic tumour will not cause varicocele, a renal tumour may do so.

Tumours of the suprarenal capsule cannot be distinguished clinically from those of the kidney; the absence of haematuria is an insufficient guide. The distinction, however, is not clinically of importance, since new growths of the suprarenal capsule, when of any consequence from their dimensions, involve the kidney, and sometimes completely efface it.

From ovarian tumours.—With an ovarian tumour the intestines lie behind; both loins are resonant; the tumour grows from below upwards, is generally more central, and either drags up the uterus, or can be felt as a swelling in the pelvis by vaginal or rectal examination. An ovarian tumour exceptionally has intestine in front of it: (i.) if of small size, the bowel may not be displaced backwards by it; (ii.) adhesions may be

formed between a coil of intestine and the front surface of the tumour, so that the bowel retains an anterior position, as in a case of ovarian dermoid with a twisted pedicle which I removed.

Enlargement of the lymphatic glands, in the near neighbourhood of the kidney, gives rise to a swelling very similar to a renal tumour. The diagnosis may be made sometimes by the independent enlargement of one or more lumbar glands not forming part of the tumour; by the abruptness of the outline of the swelling, and possibly even by a protrusion from the growth along the spermatic cord into the scrotum.

From carcinoma of the large bowel, from flatulent or faecal accumulations in the caecum, sigmoid flexure, or colon, renal tumours may be diagnosed by the absence of intestinal disturbance, of general abdominal pain and colic, of flatulent distension and intestinal obstruction.

The proximity of the colon to the kidney renders the diagnosis between nephritic colic and intestinal colic sometimes difficult. Sir William Jenner wrote: "Nephritic colic will cause loss of power in the colon, and so induce constipation, thus favouring the idea that the patient has intestinal colic. Again, collections of stools in the colon may be mistaken for an enlarged kidney; a large enema will solve all doubt on this point."

Faecal abscess or perityphlitis will be distinguished by the marked febrile disturbance, the associated intestinal symptoms, the tenderness over the front surface of the part affected, and the lower position of the swelling, which will be in the iliac rather than in the renal region of the belly.

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MALFORMATIONS AND DISEASES OF THE URETER

By HENRY MORRIS.

THE morbid conditions of the ureter requiring consideration in a work on Medicine as distinct from one on Surgery are the following: (i.) stricture and stenosis, torsion, and valves of the ureter; (ii.) ureteritis and peri-ureteritis; (iii.) tuberculosis of the ureter; (iv.) ureteral fistula; (v.) calculus in the ureter; (vi.) new growths of the ureter. Descriptions of injuries to the ureter, and foreign bodies in the ureter other than calculus, blood-clots, and little masses of mucus, are intentionally omitted.

I. STRICTURE AND STENOSIS, TORSION, AND VALVES OF THE URETER.—There are many abnormalities of the ureter to which reference only need be made in this place, because of their anatomical, not because of their clinical interest. Such are: the absence of the ureter, which is always associated with absence of the corresponding kidney; the absence of a hilum; double ureter; double renal pelvis; abnormal termination of the ureter in the bladder or elsewhere; and prolapse of the lower end of one or both ureters into the bladder. *Prolapse of the ureter* may be either acquired or congenital. When there is prolapse, the vesical end forms a pendulous pouch hanging into the cavity of the bladder, and in the female it may possibly project at the urethral aperture; the orifice of the ureter may be non-existent or of pin-hole size only; micturition is accompanied by pain; and death usually occurs from septic infection of the kidney.

There are, however, a number of congenital and pathological causes of ureteral obstruction which are of great clinical importance, because they lead to nephrectasis or ureterectasis, unless treated in good time by proper surgical means. Of this number are abnormal relations of the ureter to certain blood-vessels, stricture and stenosis, torsion, and valves. The ureter may be constricted by the renal artery or one of its primary branches, or it may be kinked by passing over the vessel. Occasionally some other artery or vein, and not the renal, may cause the constriction.

Stricture of congenital origin may cause atrophy of the kidney, or hydronephrosis, or a large saccular distension of the ureter (*ureterectasis*) which is generally situated just below the renal pelvis. Similar results in any part of the duct may follow acquired stricture. In any part of the ureter stenosis of more or less of its length may, like stricture, arise from the pathological changes following injury, the passage of a calculus, and ureteritis.

Torsion of the ureter may be either congenital or acquired. When

congenital it nearly always concerns the renal end. It may be acquired as the result of the mobility of the kidney, and the consequent twisting of the upper end of the ureter which such mobility causes. The relations of the upper orifice of the ureter to the renal pelvis become changed by hydronephrosis to such an extent that it may come to have a well-pronounced valve; or it may be gradually raised from above the lowest part of the distended renal pelvis, and a good inch or more of the tube may curve over and be firmly adherent to the outer wall of it. Torsion and valve formation are thus results as well as causes of nephrectasis.

Valves are also either of congenital or acquired origin. When congenital, their usual situation is at or near the junction of the ureter with the renal pelvis. Valves are formed in any part of the ureter as the pathological outcome of ureteritis.

Symptoms.—The result of any of these causes of ureteral obstruction may be a tumour either permanent or intermittent, fixed or very movable, and due to hydronephrosis or hydro-ureterosis, or, if septic infection occur, the contents of the nephrectasis or ureterectasis will be pus as well as urine. Males and females of any age may be the subjects of any of these conditions of the ureter. It is important to realise that the ureter itself can become dilated sufficiently to give rise to an abdominal swelling appreciable by touch and eye and having the same physical characters as nephrosis. Pain and tenderness in the flank, even when there is no tumour, are common. The kidney, whether enlarged or not, is very likely to be movable, especially if the obstruction has existed a long time. Reflex irritation of the bladder, causing frequent and painful micturition, sometimes incontinence, is frequently complained of. If the stenosis be at the vesical end of the ureter, the bladder symptoms are prone to predominate. In some instances a feeling of constriction of the bowel has existed and given rise to a misapprehension that there was stricture of the bowel itself. The uterus has been treated and the uterine appendages removed under a wrong diagnosis, and of course without any beneficial result. When the kidney is movable or a tumour exists, any of the symptoms described under movable kidney or nephrectasis may be present.

Treatment.—In every case in which from the symptoms any of the above forms of ureteral obstruction are believed to exist, an exploratory incision with the object of performing a plastic operation upon the ureter ought to be made. There should be no delay until a mobile kidney, or a tumour, is superadded to the other signs. If these cases were operated upon early there is good reason to believe that a certain number of kidneys would never become mobile, and most certainly nephrectasis and ureterectasis would be less frequently met with. It is very interesting to compare the present-day practice and teaching with the opinion expressed by Boyer in 1820: "The dilatation of the ureter is an incurable disease which almost always kills when it reaches the stage of tumour. The opening of the swelling can only accelerate death; therefore when there is reason to think that a swelling in the iliac region is caused by a dilated ureter it is necessary to guard against its being opened."

II. URETERITIS AND PERI-URETERITIS.—A study of the diseases of the kidney and of the surrounding fibro-fatty tissues shews that they are prone to extend in many instances into the ureter, and along the retro-peritoneal tissue surrounding the ureter, respectively. Thus, inflammatory affections, tuberculous disease, actinomycosis and new growths, as well as calculi, have been seen to spread from the renal pelvis into the ureter; and every kind of pathological change which takes place in the peri-nephric tissue as secondary to renal affections is excited in the peri-ureteral tissue as the result of ureteral disease.

It will be seen that the ureter and its surrounding tissues are similarly involved, as the result of extension upwards of diseased conditions of the bladder and other pelvic organs.

Urteritis.—Of primary ureteritis as an idiopathic disease we know nothing. It occurs as the result of injury, of the impaction of a calculus, or the introduction of a foreign body; but it is very rapidly followed by morbid changes in the kidney due to obstruction, if not to actual extension of the inflammation or suppuration by continuity to the renal pelvis and calyces.

Secondary ureteritis is very common, and is due to: (a) extension downwards from the kidney; (b) extension upwards from the bladder; (c) originating in and communicated from neighbouring tissues and organs, for example, the cellular tissue of the broad ligament, the uterus, ovary, or Fallopian tube, or the lymphatic glands in the pelvis or hilum; (d) extension from the orifice of a ureteral fistula.

Of the disposing causes of ascending ureteritis, some are common to both sexes, such as cystitis, growths and ulceration of the bladder; vesical atony and paralysis from spinal and other causes; and the use of septic instruments. Some are special to the male, such as phimosis, gonorrhoea, stricture of the urethra, and affections of the prostate. Some are special to the female, and these are of great importance, such as pregnancy, myoma of the uterus, carcinoma of the uterus and vagina, inflammation of the uterus, pelvic cellulitis and lymphangitis, inflammatory and suppurative affections of the ovary and Fallopian tube, and vulvitis. Also uretero-uterine and uretero-vaginal fistulas, and abnormal terminations of the ureter in the rectum, vagina, or urethra. Secondary affections of the ureter through the bladder from the genital organs below do not always involve the bladder itself in the infective process. Pregnancy or parturition, for instance, may be the starting-point of uretero-pyelitis without the occurrence of cystitis. The tendency to renal affections from inflammation spreading upwards along the ureter, especially in puerperal women, has been frequently pointed out, and is far from uncommon.

Pathology.—In ureteritis secondary to renal disease, the pathological changes vary with the nature of the renal lesion. In suppurative pyelitis the extension of the inflammation to the ureter causes its mucosa to become congested, mottled grey and red, coated with pus, and ulcerated. Its walls will be oedematous, and on section its lumen will be

diminished, especially at the level of the ulcers. In long-standing nephritis and pyelitis from the irritation of calculus, the wall of the ureter will be thickened and tough, its mucous membrane will be congested, and the peri-ureteral tissue will shew the same fibro-lipomatous condition as the perinephric tissue. In ascending ureteritis the morbid changes are extremely various, and depend on the acuteness or chronicity and on the causes of the inflammation of the inflamed organ or tissue below; on the extent to which the peri-ureteral tissues share in the inflammation; and especially upon whether the ureter has been dilated and elongated from obstruction before it has been attacked by inflammation.

A distinction must be drawn between the mechanical effects of obstruction, and the pathological changes which are due strictly to inflammation. In mechanical dilatation from obstruction the ureter is elongated, tortuous, and more or less doubled upon itself in sigmoid-shaped flexures, with thin walls between and thick sclerosed walls at the flexures; and, though increased in diameter throughout the tube, has the appearance of being constricted or strictured at the flexures. Sometimes adhesions form between the walls of the ureter at the points where it is bent upon itself, and between the walls and the surrounding tissues. In fact the ureters, as the result of obstruction and dilatation, undergo the same changes as those which occur in varicose veins. They often have a moniliform and spiral form not unlike a large umbilical cord, and are sometimes the size of the small intestine. At the points of flexure there are veritable strictures, taking the form of bands, folds, and projecting spurs, at some parts limited to small portions of the circumference, and at others almost entirely encircling the lumen. In places they succeed one another very closely and have the appearance of valvulae conniventes. They are formed by duplicatures of the wall of the ureter, not merely of the mucous membrane, at the points of bending, and are maintained by adhesions on the outside of the duct. Between these projecting folds are well-marked saccular dilatations which communicate with each other only by a narrow tortuous channel often very difficult to trace either up to the renal pelvis or down to the bladder, and twisted like the worm of a screw. These valvular formations are composed of newly formed muscular fibres. They are situated commonly at the two ends of the ureter, and often leave the middle part to form an elongated fusiform sac of considerable size, separated from the renal pelvis by a narrow sigmoid canal with prominent valves within it and along which it may be almost impossible to pass a small flexible bougie. When inflammation attacks a ureter thus altered by dilatation the mucous membrane is thickened, smooth or flocculent, mottled red and grey, with vascular streaks and dark ecchymotic patches; there are ulcers the bases of which are often ribbed by large underlying vessels. It is often smeared with sanguinolent or mucous pus, whilst desquamation, abrasion, and ulceration are going on. In the more chronically inflamed ureters, small projecting cysts in the mucous membrane are frequently present, which give rise to

the name of "vegetating or cystic ureteritis." In cases in which the urine becomes septic in the bladder, the infection spreads rapidly upwards along these dilated tubes, and soon kills the patient by suppurative uretero-pyelo-nephritis. This is the form of ureter which is produced in cases of long-standing prostatic enlargements, urethral strictures, and retention from paralysis or atony of the bladder.

Another form of ureter resulting from ureteritis is the fibrous type. In this form the most pronounced feature is the associated peri-ureteritis. The ureter is surrounded throughout its course by a thick and indurated casing of fibrous or fibro-fatty tissue which ensheathes and hides the duct, and is so intimately adherent to it in places that it is very difficult to dissect them apart. The ureter itself is thickened, shortened, straightened, and fixed. The mucous membrane shews similar changes to those in the dilated type, but it is thicker and tougher—in fact all the coats are thickened, and tend to be converted into fibrous tissue. The coats are rigid as well as tough, and the ureter presents at intervals slight enlargements, with walls sometimes of quite cartilaginous consistence. Strictures are present of an annular or cylindrical fibrous type, like the cicatricial strictures found in the urethra, and altogether different from the valvular formations formed in the dilated ureters. In extreme cases the lumen of the canal is almost or even entirely obliterated by this sclerotic change nearly or entirely throughout its length. The strictures occur in any part of the ureter, and often only one is affected, whereas in the dilated type the valvular folds occur more specially at the extremities of the canal, and it is common for both ureters to be affected and almost to the same degree. The microscopical characters of these strictures differ entirely from those of the valvular formations in the dilated ureters. There is no duplication of the walls, no hypertrophy of the muscular tissue; they consist of newly formed connective tissue, and have less muscular tissue than the rest of the walls. This type of ureteritis is that which arises from affections of the genital organs, and in old stricture cases in which the bladder is merely hypertrophied, or has been the seat of recurring cystitis of a non-infective character. It is in this fibrous type of ascending ureteritis that we meet with large unilateral pyonephrotic tumours with the opposite kidney healthy, and also with large phosphatic calculi in the kidney, the secondary formations of suppurative pyelitis.

There are cases of an intermediate type of ureteritis, in which the two pathological conditions just described are combined.

The condition of the uretero-vesical orifices in ascending ureteritis varies. They are often dilated, but by no means always so. Often they are normal in appearance and calibre; on the other hand, they are dilated, and sometimes widely so, allowing of a persistently patulous communication between the bladder and ureter.

Peri-Ureteritis.—The causes of peri-ureteritis are the same as those of perinephritis and of ureteritis, from either of which it often emanates. In para- and peri-metritis the inflammatory process has a strong preference for spreading along the ureter to the kidney, and not rarely gives rise to

peri-ureteral and perinephric abscess. In parametritis especially it is well known that the inflammatory process is very prone to follow the course of the ureter. The peri-ureteral connective tissue when inflamed becomes dense and tough, and firm masses of fibro-lipomatous tissue form, as in old cases of perinephritis. This dense tissue sometimes so compresses the ureter as to produce in places regular constrictions. In rare cases diffuse suppuration or circumscribed abscesses are developed in it. These changes, combined with the thickened coats of the ureter, give the tube the false appearance of enormous size, and enable it to be made out on palpation through the abdominal or vaginal wall.

Diagnosis and Symptoms.—The symptoms of ureteritis and peri-ureteritis are generally blended with those of inflammation of the kidney or cystitis. The ureteritis begins and advances so insidiously that it is rarely possible to diagnose it from the pyelitis or cystitis with which it is associated. If the starting-point be parametritis or perimetritis, or an affection of the uterus or one of its appendages, or an infection from a ureteral fistulous opening into the uterus or vagina, there will be a brief period before the kidney is involved, when the urine will contain albumin or pus, and tenderness will be experienced along the course of the ureter, with pain or constant aching in the iliac fossa, radiating upwards and downwards along the course of the ureter.

An accumulation of pus in a localised dilatation of the pelvic part of the ureter has been mistaken for a distended Fallopian tube and punctured, leading to a urinary fistula. Sometimes the ureter can be felt to be enlarged, through the vaginal or abdominal parietes. The urine may contain pus which varies greatly in quantity in different cases, and at different times in the same patient, especially when the ureteritis is associated with dilatation. The strictures in the ureter cause considerable embarrassment to the downward flow, and occasional intermittent crises of alternate retention and abundant discharges. In this way in some cases quite clear and normal urine is voided for days together, owing to blockage in the affected ureter, thus proving the soundness of the opposite kidney. Polyuria is frequent in uretero-pyelitis, but is characteristic of the pyelitis, not the ureteritis. When ureteritis causes colic, and blood or pus is passed with the urine, renal calculus is sure to be suspected. In a certain notable case the kidney was twice explored by operation for stone; subsequently a small hydronephrosis with very aggravated ureteritis, but no stone, was found to have been the cause of the symptoms. The general and digestive symptoms and the temperature are the same as in pyelitis and pyelo-nephritis. A very troublesome form of ureteritis is that which persists in some cases after nephrotomy, and which is sometimes associated with lumbar fistula.

Prognosis.—When the cause of the inflammation can be cured, or removed by operation, the prospect of complete recovery from the ureteritis is good. If the cause is a persistent one, so also in all probability will be the ureteritis. There is a greater probability of recovery if the inflamed ureter has not been dilated, if the inflammation does not reach the renal

pelvis, and if the latter is not dilated as well as inflamed. If the ureteritis is bilateral, as it usually is in the dilated form, the prognosis is very grave. The gravity of the case depends largely on the character of the secondary affection of the kidney—if chronic interstitial nephritis only, or an acute septic parenchymatous inflammation.

Chronic ascending ureteritis with marked pathological changes in the walls of the ureter is not likely to become inactive; it may, however, last for years, and the patient meanwhile may be in fairly good health; and if the kidney atrophies, or becomes converted into a small fibrous mass, the ureter may become a fibrous cord, and a complete cessation of all symptoms may be the result.

The treatment should be, for the most part, preventive. It consists in precaution against all causes of cystitis and infection through the bladder, in strict attention to the cleanliness of the external genitals and vagina of pregnant or lying-in women, and of the orifice of any abnormal ureteral fistula. When once the disease is established the treatment becomes so largely surgical that it would be out of place to describe it here.

III. TUBERCULOSIS OF THE URETER.—There is proof that tuberculous disease commences in the ureter, but it is commonly seen in association with renal or vesical tuberculosis or both.

Pathology.—In whatever structure of the ureter it commences, it ultimately affects all the coats, thickening and stiffening them, making them rough on both the outer and inner surfaces, and encroaching on the lumen, which is in some cases diminished, but in others enlarged. In some cases the walls undergo calcification. The valvular folds and fibrous strictures met with in other forms of ureteritis are not found in tuberculous disease. On the mucous membrane are little granular elevations, and little plaques or masses in all stages of degeneration and ulceration. In some specimens the tube is stuffed from end to end with cheesy material, and increased in diameter, and is thus very different from the contracted fibrous cord into which the ureter is sometimes converted by simple inflammation. Frequently the ureter is surrounded by a thick sheath of cellular tissue. Sometimes a secondary tuberculous abscess forms outside the tube; in other cases the tube becomes secondarily affected from such an abscess which has been set up by tuberculous disease of the vertebrae or one of the pelvic organs..

Symptoms.—The local symptoms and physical signs are the same as in other forms of ureteritis, but more pronounced. In thin persons the thickened tube is very likely to be felt through the abdominal wall; and, if the lower end is affected, through the vagina. There is likely to be tenderness and some pain along the ureter. The uretero-vesical orifice is occasionally swollen and bulging, and the mucous membrane of the bladder in the immediate neighbourhood may be thickened and congested; but by no means always are these appearances due to tuberculous invasion of the bladder, for they disappear after removal of the affected ureter. A

digital examination of the interior of the bladder in some instances will detect a thickened, patulous, and somewhat bulging ureteral orifice on the side affected. The urine has the characters described in renal tuberculosis. Micturition is frequent and intensely painful in many cases. The bladder may become infected by the tubercle bacillus through the urine, otherwise than by continuity of disease, as well as by continuity.

A renal tumour, due to tuberculous pyonephrosis or large secondary tuberculous masses, or even a hydronephrosis, may appear after a time.

Treatment.—The expectant treatment and the injection of bacterial vaccin—the new tuberculin—under the guidance of the opsonic index should be tried. When the disease is secondary to the kidney, and the kidney is excised, the whole or the greater part of the ureter should be removed with it.

IV. URETERAL FISTULA will always possess an historical interest, because it was for the relief of this condition that the first nephrectomy was successfully performed. Fistulous communications of the ureter with the surface of the body, with the vagina, uterus, or intestine, are either due to injury and disease, or are congenital.

Etiology.—(1) Congenital ureteral fistulas open on the vulva, within the vagina, and in the wall of the urethra; in the male, beneath the prepuce and in any part of the urethra; in both sexes, upon the abdominal wall, or into the rectum or some other part of the intestine.

(2) Traumatic fistulas are due to various forms of injury, such as penetrating and other kinds of wounds, punctures of a distended ureter from a mistake in diagnosis, accidental wounds during an operation, especially hysterectomy, or following an operation such as nephrectomy. In some instances a ureteral fistula has been deliberately established to save a kidney the ureter of which is obstructed, or to relieve a hydronephrosis or a hydro-ureterosis. The sloughing of the soft structures following the wearing of a pessary, or after a prolonged labour, has been a fairly frequent cause.

(3) Pathological fistulas are caused by (a) abscess in the immediate neighbourhood of the ureter and opening into it; (b) ulceration secondary to impaction of a calculus or to tuberculous ureteritis; (c) the effects of pressure, or the encroachment of a malignant growth; (d) the continuation of suppurative or tuberculous ureteritis after nephrectomy.

Morbid Anatomy.—Either one aspect only of the duct, or its whole circumference, may be engaged in the fistulous orifice. Fistulas of the abdominal portion of the ureter open, as a rule, on the cutaneous surface of the loin or front of the abdomen, or they may open into the bowel. Fistulas of the lower end of the ureter, whether congenital or pathological, open into the neck of the uterus, the vagina, or some portion of the external genito-urinary organs. A few open into the rectum. The track of the fistula may be short, and direct from the tube to the external aperture, or indirect, long, and sinuous. The walls of the fistula may be thick, tough, and fibrous, or lined with a soft and readily

bleeding granulation-tissue. It is often difficult to locate the point of communication with the ureter of a fistula which has a cutaneous orifice.

Symptoms and Diagnosis.—A ureteral fistula gives exit either to urine, urine and pus, or pus only. This will depend upon three things: (1) if the ureter be in direct communication with the kidney as well as with the external orifice, urine will escape; (2) if the ureter be in direct communication with the kidney and open into an abscess cavity or a pus-secreting sinus, pus will escape as well as urine; (3) if not in communication with the kidney, pus only will escape, unless urine is projected upwards along the ureter in contraction of the bladder—a rare but actual occurrence. If urine escapes, it may flow continuously, or *guttatim*, or at intervals, as when regurgitated from the bladder. If the external orifice become stenosed, or heal over, or be filled by granulations, urine and pus are retained, an abscess is likely to form, and fever and rigors to occur. Urteritis and pyelonephritis are probable, but not necessary complications.

The diagnosis between a fistula communicating with the ureter and one opening into the renal pelvis is often quite impossible. The diagnosis between a fistula of the lower end of the ureter opening into the neck of the uterus or into the vagina, and a fistula of the bladder opening into these passages, is ordinarily a simple matter. The bladder should be emptied by catheter, then the patient should sit for an hour or more upon a commode. At the end of the time, the urine which has escaped into the commode should be measured, and the catheter should be again passed into the bladder, and the urine withdrawn through it should be measured. If the two lots of urine are about the same in quantity, there is the strongest proof that the fistula is ureteral, and involves one ureter only. Whether the fistula involves the bladder only, or both the ureters and not the bladder, the whole of the urine will, in the sitting posture, escape by the vagina into the commode. The urine flows from a ureteral fistula in every position the patient assumes. This is not invariably the case with vesico-uterine and vesico-vaginal fistulas. The injection of a coloured fluid into the bladder will cause no escape at the fistulous opening when the ureter is at fault, but a free and immediate escape when the bladder is the seat of the fistula. This test, however, is not quite infallible, as the coloured fluid has been known to escape from a fistula of the ureter quite near the bladder. In general terms it may be stated thus: if urine flows steadily from the vagina when the bladder is emptied, if the urine from the vagina differs much from that passed from the bladder, if the amount flowing from the vagina equals that passed or withdrawn from the bladder, and if a probe passed into the fistula cannot be touched by a sound passed per urethram into the bladder, there is the strongest evidence that the fistula is ureteral and not vesical.

Prognosis.—There is little tendency to spontaneous cure, except when one side only of the circumference is involved. Some of those which follow operations on the kidney, provided the ureter below is patent, as

well as a very few of those which follow abscess or sloughing within the pelvis, and open into the vagina, also heal spontaneously after an indefinite length of time. When the fistula opens into the neck of the uterus, the cervix uteri may be so altered by inflammation and ulceration as to give the impression of carcinoma.

The general health may keep quite good, unless, from septic conditions or from the cicatrical contraction of the tissues around the fistulous orifice, uretero-pyelo-nephritis, or pyonephrosis, or pyo-ureterosis result.

Treatment is either palliative or operative. The palliative treatment consists in scrupulous attention to the hygienic condition of the patient, and to maintaining the aseptic condition of the parts about the fistulous aperture; and also in the employment of such general and mechanical measures as will diminish as much as possible the mental and physical annoyance and local irritation of the constant escape of urine. The operative treatment is very varied, different for different conditions and cases. Though of the greatest importance for the comfort and safety of the patients, the reader must be referred to special treatises on the surgery of the kidney for information with respect to it.

V. CALCULUS IN THE URETER.—Calculous concretions are rarely formed in the ureter, and, when originating therein, are composed of phosphates deposited above a stricture, or upon an ulcerated surface, or formed around a foreign body introduced into the canal. Boyer mentions a case in which a pin which had gained entrance into the ureter became encrusted with salts, and gave rise to an abscess.

By calculus in the ureter is commonly meant that a calculus formed in the kidney has become impacted in the ureter. When a stone becomes impacted, it may remain *in situ* for an indefinite time. The points at which impaction is most likely to occur are: (a) at the renal pelvic orifice; (b) within the first inch of the upper end; (c) where the ureter enters the wall of the bladder; and (d) where it crosses the brim of the true pelvis. A calculus also becomes lodged at other points, and, in fact, there is no part of the duct at which a stone may not be arrested; the curved course, and not the narrowness of the lumen, affords the explanation of impaction a little below the pelvic brim, where there is a natural fusiform slight dilatation of the tube. Sometimes the tube is found packed with separate calculi from end to end. In one case I removed nine calculi of considerable size and faceted on their opposed surfaces, from the lower end of the ureter of a patient whose kidney I had previously excised on account of extreme calculous pyonephrosis. In rare cases the ureter has been found occupied by one continuous calculous mass which had formed a complete cast of the tube.

The characters of the calculi impacted differ in size and form, as has just been stated. They differ, too, in composition, as we should expect they would do from their originating in the kidney. Some are composed of uric acid and the urates, others of calcium oxalate, and others again are

phosphatic. The rarer calculi of cystin and xanthine might also become impacted, especially cystin, which are sometimes very numerous in the same individual and of very varying sizes. Any calculus, once it becomes impacted in the duct, is liable to have a coating of phosphates formed upon it, or to increase by the superposition of fresh salts of the same kind as the rest of the stone. The gravity of the consequences which arise from impaction are by no means proportionate to the size or number of the calculi impacted. A single stone no larger than a pea, or, still less, a hemp-seed, and weighing no more than one grain and a half, has not infrequently been the cause of death. Usually the size does not exceed that of a cherry-stone, a horse-bean, or a date-stone. In some instances, instead of a definite calculus, there has been found a soft mortar-like calculous paste. Phosphatic and oxalate calculi are apt to become impressed into the mucous membrane by their rough tuberculated surfaces, and require to be dug out before they are freed; others, composed of uric acid, though they may be tightly compressed by the ureteral walls, are not adherent and may be made to glide upwards and downwards above the point at which they cannot pass. Some move like a ball-valve from the renal pelvis into the top of the ureter and back again; some, when impacted at the lower end of the duct, project partially through the ureteral orifice into the bladder. Urine travels past the impacted calculus in many cases, and may make a gutter-like depression on its surface. Le Dran quotes a case in which there were several calculi, weighing together three ounces, impacted in the middle part of a ureter, and yet urine found its way along the duct between and past the stones.

Pathological Changes.—Abscess or diffuse suppuration of the periureteral tissue may result from perforation of the ureter by the stone.

Above the impaction there may be sacculation, thinning, and dilatation of the walls of the ureter; inflammation, oedema, and suppuration. Perforation of an ulcer or bursting of the thinned and dilated tube may occur. Below the impaction the tube may be inflamed, thickened, sclerosed, or converted into a mere fibrous cord. The whole ureter has been thus changed into a cord when a stone has blocked its upper end.

The changes caused in the kidney are those due to obstruction, and have already been described in the various sections on the kidney. Briefly they may be enumerated as atrophy, hydronephrosis, pyelitis, pyelonephritis, polycystic disease, and, if suppuration occur, suppurative pyelonephritis or pyonephrosis.

Symptoms.—The general and local symptoms are the same as those of renal calculus. In thin persons the calculus, when arrested just above the brim of the pelvis, has, in some instances, been felt through the abdominal wall. When in the lower part of the duct, the hard body has been felt on vaginal or rectal examination with the finger, and when projecting into the bladder, by the sound.

As soon as impaction has occurred there is generally sudden pain followed by haematuria or anuria, and the subsequent symptoms will

largely depend upon whether the obstruction is complete or incomplete, and whether the opposite kidney is healthy, or absent or destroyed. If the obstruction be incomplete, or intermittent (as when a calculus at the upper end of the duct acts like a ball-valve), a hydronephrotic tumour will probably follow in time. If the obstruction be complete, or nearly so, and the opposite kidney be defective, anuria, with all its alarming consequences, will result. It is in these circumstances that a minute calculus, no larger than a hemp-seed, becoming impacted and imbedded in the mucous membrane of the ureter, together with the oedema which it causes in the tissue around, has led to fatal anuria and uraemia. Attacks of profuse haematuria constitute another danger that may arise from a small calculus. I have recorded one such case in a young married lady who nearly lost her life in this manner before the calculus was successfully removed. Intermittent and copious discharges of pus, followed by the disappearance of a swelling in the renal region, have sometimes been the consequence of an impacted calculus in the ureter; and in one case carcinoma appeared in the affected kidney. Prolapse of the ureter across the cavity of the bladder, and out through the urethral orifice as far as the vulva, was observed in one case recorded by Davies-Colley. Such a condition should immediately suggest the probability of an impacted ureteral calculus.

Diagnosis.—It is impossible in most cases to diagnose a stone in the ureter from a stone in the renal pelvis or calyx, except by means of the *x*-rays. This is easily understood when we recall how often the pain of renal calculus is referred, not to the kidney, but to some point along the course of the ureter, or to the bladder, ovary, testis, or elsewhere. So also the pain of a stone in the ureter may be similarly transferred, and to the kidney itself as well as to the other organs mentioned. Unless a calculus in the ureter can be felt through the abdominal parietes, the rectum, or vagina, or detected projecting through the ureteral orifice into the bladder by the finger or sound, its precise position cannot be ascertained except by the *x*-rays, or an exploratory operation.

From *cystitis* it would be readily distinguished if more attention was paid to the character of the urine, and the deplorable error of treating renal and ureteral calculus for cystitis would then not be so frequently made. In calculus the urine is more or less acid, even though it contains blood and pus; in cystitis the urine is alkaline, and deposits a quantity of stringy offensive mucus, and has, especially after standing, a strong ammoniacal odour. A calculus which projects at the uretero-vesical orifice may, of course, give rise to cystitis. From *ureteritis* calculus may be distinguished by the sudden onset of the symptoms, and the absence of other causes of inflammation. In both conditions there may be marked tenderness over the ureter at the brim of the pelvis. Ureteritis is often set up by the impaction of a calculus in it. A nodular enlargement of the ureter with thickening of the peri-ureteral tissue, if felt through the parietes of a thin person, might suggest a calculus in the

ureter. In tuberculous disease of the ureter, tubercle bacilli are likely to be found in the urine.

From a prolapsed and inflamed and adherent ovary a calculus impacted in the ureter may be difficult to diagnose. There are at least two instances on record in which the mistake was made, and an operation was undertaken on the diagnosis that the symptoms were due to an inflamed and prolapsed ovary. Between an *encysted vesical calculus* and a calculus impacted in the vesical portion of the ureter no differential diagnosis can be made clinically. There are, however, certain differences which may be detected on digital exploration of the bladder, but these are only likely to be sought for by the surgeon. A reference to works on the surgical affections of the kidney is recommended.

Prognosis.—*As regards life*, this depends on the condition of the opposite kidney, and on the secondary effects which the obstructed ureter may have on the kidney of its own side. When the kidney of the opposite side is normal and the kidney of the affected side merely atrophies, all will go well. If the opposite kidney is defective, and that of the recently involved side either atrophies or suppurates, death will result.

As regards the kidney the prognosis is very unfavourable if the impaction and obstruction continue, for then the kidney must either atrophy, become distended, or suppurate.

Treatment.—No medicinal treatment is of any use; nothing in the way of drugs, baths, massage, or diluents affords any hope of saving life if the only sound kidney is affected by the impaction, or of preserving the integrity of the kidney involved, when a stone is impacted in, and not simply passing down, the ureter. Surgical assistance should be obtained at an early stage. If this is done, there is an excellent prospect of saving both the kidney and the life of the patient by means of one of the several methods of extraperitoneal ureterotomy. What the precise method of operation to be selected will be, depends on the section of the ureter in which the impacted stone is.

Foreign bodies derived from the renal pelvis, such as sabulous matter, hydatids, little masses of pus or mucopus, or tuberculous caseous material, sometimes become impacted in the ureter, and give rise to the same effects upon the kidney as any other kind of ureteral obstruction. Blood-clot derived from the kidney or from an injured ureter sometimes permanently blocks the tube. The changes which take place in blood-clot in a ureter are the same as those which occur in a thrombosed vein; it may become partially or entirely absorbed, or organised into a fibrous cord, or may suppurate or decompose. If haemorrhage continues after the clot is arrested in the ureter, haematonephrosis follows. (See p. 683.)

VI. NEW GROWTHS OF THE URETER.—Primary tumours of the ureter are extremely rare, and do not occur more than half as frequently

as primary tumours of the renal pelvis. Cystic and solid, innocent and malignant new growths originating in the ureter are recorded.

Cysts.—The cysts are for the most part parasitic and due to psorospermesis. They are thickly studded on the mucous membrane, and generally extend into the renal pelvis and sometimes into the bladder. They are yellowish or greenish brown, or greyish-white in colour, of the size of a millet- or hemp-seed, and contain colloid material in which the coccidia are found. (*Vide "Ureteritis Cystica," Vol. II. Part II. p. 827.*) Some cysts are doubtless of glandular origin, being enlarged mucous cysts.

The symptoms recorded in one case were pain, frequent and painful micturition, and severe haematuria; death occurred on the seventeenth day after the onset of the illness. Hydronephrosis, chronic interstitial nephritis, and ureteritis have been produced in other cases.

Papilloma originating in the ureter may be limited to the tube, or spread upwards into the renal pelvis if in the upper end, or downwards and project into the bladder when in the lower end. The growth is in some cases diffused throughout the tube; in others both extremities, but not the intervening part, are affected. Though most of the recorded papillary tumours were at the outset simple, several have been known to become malignant, or to recur as malignant new growths after removal.

Sarcoma.—Round-celled and myxo-sarcoma have been found in the ureter, extending over a great part or the whole of the tube, but the situation of origin appears to have been doubtful. In one the renal pelvis was invaded; in another the whole ureter was probably invaded from without, and a polypoid excrescence projected through the ureteral orifice into the bladder.

Carcinoma, especially of the villous epitheliomatous type, is the form most frequently found in the ureter.

The mucous membrane of the ureter sometimes undergoes a modification, indeed such a marked change as to cause it to acquire characters closely allied to those of the skin—so far, at least, as the cutis vera and epidermis are concerned, but, of course, without the formation of any true cutaneous appendages. This conversion under prolonged irritation explains the occurrence of squamous-celled carcinoma which has been observed in the ureter as well as in the renal pelvis. Carcinoma of the ureter is highly malignant. The lymphatic glands, pleurae, lungs, peritoneum, and liver, as well as the kidneys and bladder, are very prone to be the seats of metastases.

Etiology.—Primary new growths of the ureter occur in middle and late life, and in both sexes, but in men more often than in women. In several cases urinary calculi have been present, and embedded in or surrounded by the new growth. In one case carcinoma commenced in a congenital abnormality of the ureter—namely, a diverticulum of its lower end. In one case primary cancer of the ureter was mistaken for an osteosarcoma springing from the ilium.

Symptoms.—Haemorrhage, tumour, and pain are the three leading symptoms of all these ureteral new growths. *Haematuria* is most

frequently the earliest symptom ; but when it is not, it is rarely absent throughout the whole course of the case. It may be intermittent. The earliest symptom, when not haematuria, is tumour. In comparison with the number of cases, it is more frequently present as a result of ureteral than of renal neoplasms. In some cases the tumour is caused by the ureteral growth itself, and it then occupies the umbilical and lumbar regions. When it is renal in origin, it will generally be hydronephrotic in character. Pain may be slight, or even absent, throughout ; but it is, on the other hand, often an early and even the earliest indication. Severe pains in the loin and thigh have been felt at the outset. They may be recurrent and the effect of blood-clots passing along or becoming impacted in the ureter. Haematonephrosis and ureterosis may occur if the ureter is blocked and the haemorrhage continues. Pain, however, has been absent, even when enormous elongated blood-clots have filled and traversed the ureter. The urine may be unchanged except for the presence of blood, but careful and repeated examinations may lead to the detection of fragments of the growth, or of numerous epithelial cells which may indicate the nature, though not the precise seat, of the disease. A papillary process, or a polypoid offset of a malignant new growth, may be seen with the cystoscope projecting into the bladder through the ureteral orifice.

Prognosis and the pathological changes may be considered together, because the former depends upon the latter. The propagation by continuity and by diffusion of the simple papillomas, and their tendency to become malignant, make the prognosis in their case unfavourable. The diffusion and extension along the duct itself and the generalisation of the metastases in malignant disease are the sources of danger in sarcomatous and carcinomatous new growths. The secondary lesions of the kidney from nephrectasis and suppuration are dangers common to both the simple and the malignant tumours.

Treatment. — The only treatment offering a possibility of cure, whether in the non-malignant or the malignant new growths, is excision of the portion of the ureter containing them. The reader is referred to works on the surgery of the kidney for the description of the details of the operative treatment.

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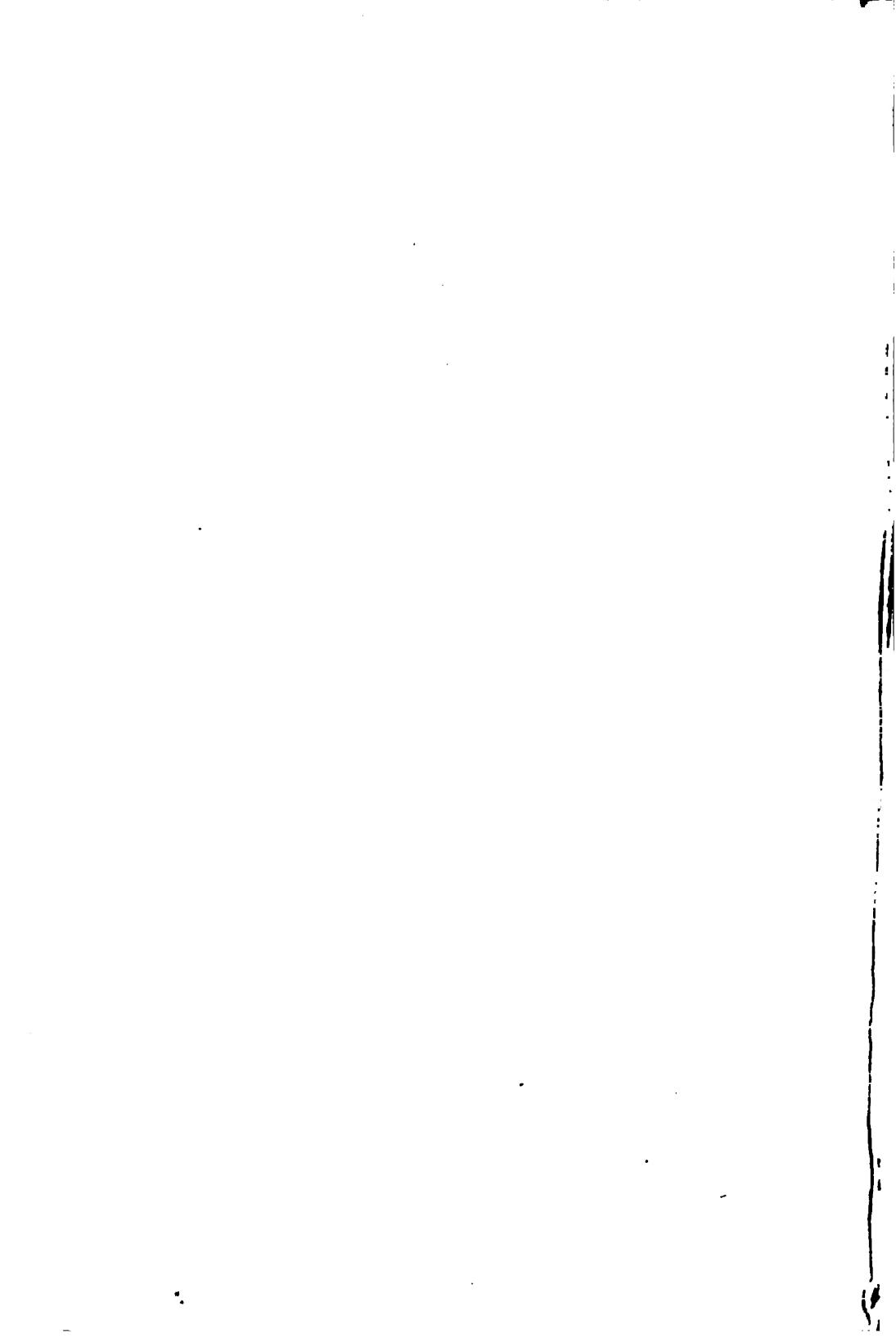
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